A THIRTY-YEAR SURVEY OF ACUTE INTUSSUSCEPTION IN CHILDHOOD

269 CASES

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THIS paper is a survey of all cases of intussusception in childhood which have been admitted to a general hospital during the thirty years 1929–58. For the purposes of this series, childhood has been arbitrarily defined as the period from birth to 5 years.

Mortality has decreased in the period under review (table I). The apparent rise in the second decade is

TABLE I—CASES AND MORTALITY

—	Number of cases	Deaths	Mortality %
1929–38	91	16	17·6
1939–48	76	20	26·3
1949–58	102	9	8·9
Total	269	45	16·7

probably the effect of the first two years of the war, when there was a general disruption of the medical and hospital services. Though the improvement since 1929 is gratifying, there are still no grounds for complacency.

It is interesting that, of a total of 22 cases requiring resection, 7 were operated on between 1929 and 1948 with 6 deaths; but, between 1949 and 1958, a further 15 resections were performed with only 4 deaths.

The mortality for the whole of this series was 16·7%.

Though this disease affects some of the healthiest of our child population, it has seldom been reviewed in Britain. In Australia, on the other hand, where great attention has been paid to this condition since the turn of the century, Hipsley (1926) and Vickers (1926) were able to record mortality figures of 5% and 11·5% respectively as long ago as 1926.

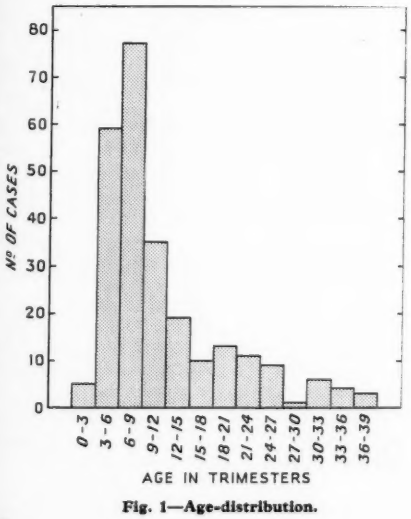

Fig. 1—Age-distribution.

We feel that a further survey is due, if only to emphasise the importance of early reference to hospital of any suspicious case. Even today many patients are referred to hospital at a distressingly late stage of the disease.

This series consists of 269 cases, with 45 deaths.

Age

The age of the patients in this survey closely follows that in most other series, the largest group consisting of children between the ages of 3 and 9 months (fig. 1). As would be expected, the mortality falls with increasing age; it was 31% at 0–6 months, 14% at 7–12, and 0·7% at 12–24.

Sex

There were 176 boys and 83 girls, an approximate ratio of 2/1—as in most other recorded series. An exception was the Newcastle series (Morrison and Court 1948), covering the period 1944–46, where 45% of the cases were girls. The mortality in our series did not vary between the sexes.

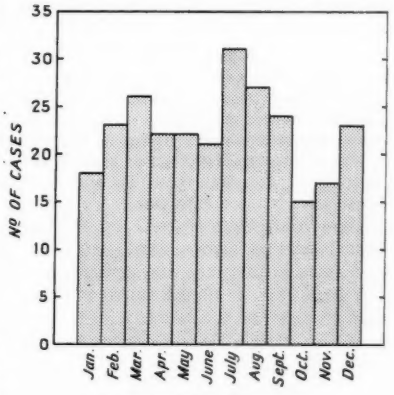

Fig. 2—Seasonal distribution.

Seasonal Incidence

The number of cases seems to vary considerably from year to year, ranging from 4 in 1935 to 15 in 1956. The incidence (fig. 2) agrees roughly with that given by Strang (1959), and is greater in the spring and summer.

Ætiology of Intussusception

Though in adults 80–90% of the cases have a definite causative lesion, the ætiology of this condition in children remains largely hypothetical.

In a few children, a definite lesion is found to be the cause—for example, a Meckel's diverticulum, a polyp, or even intestinal reduplication. In this series, the intussusception was due to an inverted Meckel's diverticulum in 4 cases; and in another case an intussusception recurred with the appendix stump forming the apex, appendicectomy having been carried out at the first operation. In the remaining 264 cases, a definite cause was lacking.

Dietary changes or indiscretions have been incriminated; but these, because of the wide variations in the management of infant feeding, are very difficult to assess. The extent to which unofficial supplements are added to the feeds remains unknown, particularly when mothers are working and children are left in the care of relatives or friends. In these circumstances, lack of general cleanliness and sterility of feeds may provide a source of infection. Mr. C. Vincent Patrick tells us that he knows of no privately treated cases of intussusception in this area for many years.

Nothnagel in 1898, after experiments with rabbits, popularised the hypothesis that intussusception results from intestinal spasm, and he suggested that a contracted area was propelled onwards like a bolus of food. With this hypothesis as a basis, other causes of spasm have been put forward. It has been suggested that the change from milk to a more solid diet may cause intestinal irritability, and thereby spasm. Spasm undoubtedly occurs in gastro-enteritis, and in a few cases a recent history of intestinal upset can be obtained. More recently, a delay in the development of the inhibitory sympathetic system to the small bowel has been blamed, producing spasm in the ileum and relaxation of the ileocæcal valve.

Linked with, and added to, the concept of spasm must be an abnormality of motive power in the shape of exaggerated or perverted peristalsis. Bowel movement may be exaggerated by changes in the volume of bowel content, or by the action of drugs or noxious agents within its content, or via the blood-stream, provided infection is not severe enough to produce paralysis and the dilatation of ileus. Grossly abnormal peristalsis must sometimes take place or else a retrograde intussusception would be an impossibility.

A child of 12 months had a history of being off colour and irritable for seven days, five days diarrhœa (chiefly after meals), and vomiting with screaming attacks for four days. Two days before admission a questionably blood-stained stool was passed, after which there was no bowel action. At operation, she was found to have three separate intussusceptions—an ileocolic, a retrograde colocolic, and an advancing colocolic. These were reduced with ease.

This child illustrates well the beginning of a prodromal gastrointestinal upset, with ensuing derangement of peristalsis leading to intussusception. Recently a child, operated on in another hospital of this group, had no less than 15 separate intussusceptions, which must indicate a most widespread peristaltic upset (Hadfield, personal communication).

It is suggested that infection plays a large part in the production of this exaggerated peristalsis, and possibly in the origin of local spasm by the irritant effect of swollen Peyer's patches and enlarged mesenteric glands. Peyer's patches are difficult to recognise at operation when the bowel is reduced and œdema from strangulation involves the whole region of the apex. In a case coming to necropsy shortly after reduction, definite hyperplasia of lymphoid tissue was seen, with bulging into the lumen of the bowel, and in places a pseudopolypoid appearance. Against this hypothesis of local tumour formation by hyperplasia of Peyer's patches, the experience of surgeons operating on cases of Peutz-Jegher syndrome has been that the polypi responsible for the intussusception have been 1–1½ in. in diameter—large enough to cause obstruction of the bowel. Similarly, other small-bowel tumours causing intussusception do not do so until they are so big that they cause obturation. If Peyer's patches are to cause intussusception, they must have enlarged sufficiently to obstruct the bowel almost completely.

Enlarged mesenteric glands are present in many cases, and they appear to precede the intussusception rather than to follow it. They have often been found in cases operated on four to six hours after onset of the illness.

In this series, pyrexia has been a feature on admission. Some pyrexia would perhaps be expected in any illness producing irritability, screaming, and dehydration; but of the last 63 cases, 35 had a temperature of over 99·5° and in 12 it was over 100·5°. This pyrexia is not in accord with most standard descriptions where the temperature is stated to be normal or subnormal, or else is not mentioned at all, but agrees with the findings of Morrison and Court (1948).

An analogy can be drawn between the findings in intussusception and those in nonspecific mesenteric adenitis.

In the latter, an older child, commonly with a history of recent upper-respiratory-tract infection or tonsillitis, is admitted with high temperature and attacks of colicky abdominal pain, sometimes of extreme severity. Between attacks of colic, there is entire freedom from pain and the child may be found sitting up and taking notice, or even playing with toys. Tenderness, the site of which alters with position, can be elicited, and auscultation will often confirm the presence of exaggerated peristaltic sounds. These signs suggest hyperactive bowel, and the tenderness might well indicate an area of local spasm.

At laparotomy, there is discrete enlargement, usually more marked in the ileocæcal region, of the mesenteric glands of the ileum. A varying amount of free serous fluid is present in the abdomen. The ileum may appear normal or may show a mild serous hyperæmia. Occasionally, it may be the seat of palpable œdema of the whole thickness of the bowel wall. The appearances of the lymph-nodes and of the bowel are of inflammation, suggesting a response to infection.

The symptoms and intra-abdominal findings in these two conditions suggest a common causative agent, but it does not explain why intussusception is less common in older children.

Some other factor must be present, and the only other variable appears to be the increased diameter of the bowel in older children. Zachary (1955) suggested that the intussusception would be tighter in a younger child because of the smaller bowel diameter. He was able to reduce more cases by barium enema in infants over 6 months old than he could in those under 6 months, irrespective of length of history. In our series, 64 cases were under 6 months and 9 of these (14%) required resection. Of the remaining 205 cases, 13 (6·3%) required resection. A reasonable assumption is that intussusception is rarer when the bowel lumen is large, because spontaneous reduction probably takes place more readily.

Finally, anatomical factors may play a part. In many cases of ileocolic or ileocæcal type, abnormal mobility of the ascending colon and cæcum is noticed, and this may influence the final outcome. In recent cases, more critically examined at operation, it has appeared that the greater the mobility, the less likelihood there is of compression of the mesentery with consequent strangulation; conversely the more difficult cases to reduce have been those with a relatively fixed cæcum. The prominent and protruding ileocæcal valve of infancy has received its share of the blame, and clearly it might form the apex of an ileocæcal intussusception. In this series, however, the ileocolic type has been much more common than the ileocæcal type.

Apparently no one factor can be held responsible for intussusceptions at all levels of the intestinal tract.

Clinical Features

In assessing the symptoms in this series, we have often found it extremely difficult to pinpoint the onset of intussusception in the midst of a gastrointestinal or respiratory illness. We have tried, however, to take the point at which symptoms became progressive and relentless rather than that marked by intermittent attacks of colic or vomiting which seemed to signal the onset of illness in a proportion of children.

The length of history does not always seem to corres-

pond with the severity of the intussusception, the degree of intestinal obstruction, or the distance the apex advanced.

Some cases with short histories and a relentless course have come to resection within twenty-four hours; while in others with long histories and slight constitutional signs, intussusceptions have reduced easily. These two groups do not seem to be confined to any particular type.

Fig. 3 shows the series divided into three groups according to the length of history, where this could be accurately obtained. 80 seems a very high figure for cases with a history of more than forty-eight hours, and analysis by years shows that the number of late cases has actually increased over the last few years of the survey. This is perhaps surprising, because doctors refer their patients to hospital earlier than in the past. In 1929–38, 76% of cases arrived in hospital within twenty-four hours of the onset of the illness; but in 1949–58, the percentage of cases arriving within twenty-four hours had fallen to 57.

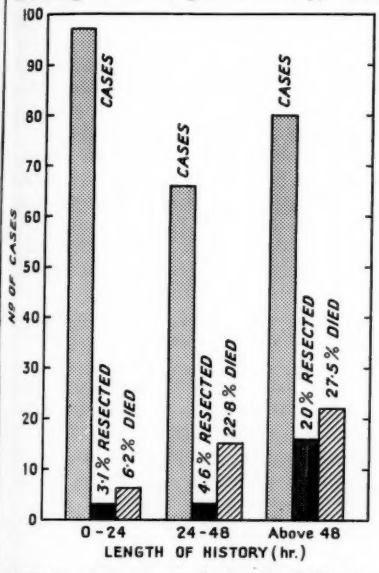

Fig. 3—Numbers of cases by length of history, with the resection-rates and mortality-rates.

The resection-rate increases only slightly with the length of history, but the death-rate rises considerably after the first twenty-four hours. After forty-eight hours, there is little further increase.

To the recognised tetrad of symptoms—pain, vomiting, rectal bleeding and palpable mass, there is little to add.

Pain is difficult to measure or assess in young infants; and, while many were in obvious pain, screaming with the knees drawn up, some lay quietly. The only evidence of pain has been a slight restlessness and increase in pallor, associated with a hardening of the lump under the palpating hand. Pallor is very common, not often mentioned in reports, and might indeed be added to the tetrad.

Rectal bleeding was found in 161 out of 190 cases (84·7%). In 184 cases a mass was palpable in 157 (85·5%), either abdominally or per rectum.

In 882 published cases, we have noted that blood was present in 80% and an abdominal mass in 73%. The apex was felt per rectum in 17%.

In our series, a palpable mass was found per rectum in 28 cases (10·5%); and in one case, no less than 5 in. had emerged from the anus, the apex being the ileocæcal valve. This was reduced and the child recovered. The mortality-rate for those cases where the apex was palpable in the rectum is slightly higher than that for the whole series.

Types

Intussusceptions may be divided into groups, the nomenclature of which indicates (1) the area of bowel at which invagination starts, and (2) the area of bowel receiving the invagination.

Ileoileal

There were 14 cases (5·6% of the total). 7 of these required resection and 5 deaths occurred (3 resections and 2 simple reductions). This was the most lethal type, as has been noted in other series. Factors leading to this high mortality-rate are the common absence of a palpable mass, often masked by abdominal distension, and the later appearance of blood in the stool; both of which contribute to delayed admission. Of our 14 cases, no less than 8 had symptoms lasting over forty-eight hours. Blood was present in only 7, and a mass was noted in only 3.

Ileocolic

This group forms the largest of the series—84 cases (31%). Here the apex was found to have originated at points varying from $^1/_2$ to 9 in. above the ileocæcal valve, and then passed onwards through the valve. In 23 cases, where measurements were recorded, the average distance of the apex from the valve was $3^1/_2$ in. Of these 84 cases, 5 required resection. There were 11 deaths (13%) of which 4 had been resected.

Ileocæcal

Here the valve itself forms the apex, advancing into the ascending colon, and dragging in more ileum as it advances. There were 51 cases (18·9%), and 3 cases required resection. There were 10 deaths (20%), including 1 which had been resected.

Cæcocolic

The apex is formed by the caput cæci and, after reduction, an œdematous dimple may be noted on the most pendulous part of the cæcum. This is perhaps the most difficult type of intussusception to explain, occurring as it does from the " backwater " of the most inert part of the large bowel. There were 15 cases of cæcocolic intussusception—5·6% of the series. None of these required resection, and there were 3 deaths.

Unclassified

Insufficient details were obtainable in these cases to be able to classify them. There were 75 cases (28% of the series). 4 cases required resection and out of 12 deaths (16%), 2 had been resected.

Compound (or Ileo-ileocæcal)

Here an ileoileo intussusception stops at the ileocæcal valve, and the valve then advances, adding two new layers to the three layers of the original ileoileal type. It might well be thought that with the larger intussusceptum, earlier symptoms and earlier strangulation would occur. In fact, of the 10 cases in this series, only 3 were admitted with histories under forty-eight hours; 3 cases required resection, and 1 died after simple reduction.

Multiple

There were 2 cases with separate intussusceptions; 1 has been mentioned, and the other was an ileoileal intussusception, entirely separate from an ileocolic intussusception.

Management

Since Hutchinson performed the first recorded operative reduction in a child in 1871, this has been the standard procedure in many centres throughout the world. In an endeavour to reduce the high mortality, methods of reduction by hydrostatic pressure were developed. Hirschsprung (1905) recorded a series of 107 cases, with a mortality of 35%, after hydrostatic reduction; in other authors' hands, the operative mortality at this time was in the region of 90%.

Since then, the mortality has been reduced for both operative and non-operative methods of reduction.

TABLE II—MANAGEMENT

—	Cases	Deaths
No treatment possible (child in extremis)	5	5
Spontaneous reduction	6	1*
"Closed" manipulation	2	0
Successful reduction by barium enema	5	0
Laparotomy and reduction	229	29 (12·7%)
Laparotomy and resection	22	10 (45·4%)
Appendicectomy at time of reduction	34	1
Meckel's diverticulum forming apex:		
Left in situ	2	1
Excised	2	1

* Died on third day. Necropsy revealed recent ileoileal intussusception.

Hipsley (1926) recorded a series of 100 cases treated initially by hydrostatic pressure, and operation if this failed, with a mortality of 5%. His cases had an average length of history of only seventeen hours. In more recent years, comparable results have been recorded for cases of less than twenty-four hours' duration, treated either by operation or hydrostatic pressure. In our series, cases seen within twenty-four hours of the onset show a mortality of 6·2%.

In this hospital, in the thirty-year period under review, the management has been mainly surgical until recent years (table II).

5 children were in extremis on arrival. 1 had been ill for ten days; 1 for seven days; and in the other 3 no accurate history was obtainable.

Judging by the signs and symptoms, 6 cases had undergone spontaneous reduction. In 2 of these, evidence of recent reduction was obtained at laparotomy.

2 cases were reduced under anæsthesia, using a method of combined abdominal and rectal manipulation without laparotomy. This method might be dangerous in unskilled hands, particularly in cases with a history of over twenty-four hours; and, if there is any doubt about the reduction, laparotomy must still be done.

Laparotomy and reduction were performed in 229 cases (85%) with a mortality of 12·7%. Reduction was achieved in some cases with considerably difficulty, and serosal or seromuscular splits were required for repair.

Resection proved necessary in 22 cases (8·2% of the total), with a mortality of 45%. In these 22 cases, the average length of history was fifty-seven hours, and in only 3 cases was the history less than twenty-four hours. This brings out again the need for early diagnosis. A careful and quick resection is preferable to a prolonged attempt at closed reduction; and, in our operative records, where "great difficulty" or "serosal splits repaired" have been mentioned, the mortality has been higher. Experience and judgment are two essential prerequisites in determining when to abandon attempts at reduction and resort to resection.

The procedure for dealing with irreducible intussusceptions in seriously ill children remains a problem. Gross (1953), Bentley (1954), and Jones (1953) have advocated a two-stage procedure; the first stage being exteriorisation, with or without suture of the loops, and the second stage being closure of the ileostomy. All writers stress the importance of carrying out the second stage at about forty-eight hours, or as soon as possible after this.

In our series, exteriorisation was carried out only once, in a severely ill child of 4 months with a ninety-six-hour history. This child, operated on in 1940, died four hours after operation.

A Witzel proximal ileostomy was carried out once in a child who was grossly obstructed because of a compound intussusception of seventy-two hours' duration which required resection. The child made a satisfactory recovery. This procedure, which we are using much more often in adult cases of obstruction and ileus, seems to be a useful manœuvre in the grossly obstructed child in order to decompress the dilated bowel and spare the anastomosis.

We have no experience of other operative procedures for the irreducible intussusception, and there are no cases in this series. A short-circuit ileotransverse colostomy, leaving the intussusception to slough and be passed per rectum, has been suggested; but this leaves a gangrenous length of bowel in the abdomen of an already sick child, with the danger of peritonitis from leakage between the entering loop and sheath. Incision of the sheath to aid reduction, or to enable the intussusceptum to be excised, involves suturing œdematous and congested bowel, and has the risk of contamination through the open bowel lumen. Both these procedures offer little, if any, saving of time over resection and anastomosis; and, where time is important because life is in danger, we would advocate exteriorisation and temporary ileostomy.

Appendicectomy was performed at the time of reduction in 34 cases: the 1 death was probably unrelated to the additional surgical procedure. In some cases there is frank gangrene of this organ—a most vital indication for its removal. In many others, however, the appendix shows some œdema and a greater or lesser degree of congestion—changes, in fact, similar to those in the bowel wall in the region of the reduced apex. These changes will probably subside in the appendix just as they do in the bowel, and it seems illogical to remove this organ, having reduced one intussusception, only to leave another miniature one in the buried appendix stump.

In 4 cases an inverted Meckel's diverticulum formed the apex. Meckel's diverticula are usually stated to be the cause of intussusceptions in older children. The ages, however, of these 4 children were 7, 18, 24, and 30 months. If the intussusception is reducible, the question of removal arises again. This is perhaps a more difficult problem. Local removal of a diverticulum forming the apex will involve sewing œdematous and congested bowel and, provided viability is assured, it would seem safer to leave this abnormality. In 2 cases in this series the diverticulum was left in situ; there was 1 death from peritonitis due to perforation of the diverticulum. One diverticulum was excised locally and the child did well; one was irreducible and was removed by hemicolectomy. The risk of recurrence after leaving a reduced Meckel's diverticulum must exist, but its incidence can only be assessed by experience with a larger number of cases than we have been able to obtain.

Recurrences

10 cases have recurred, at very variable intervals after the first operation (table III).

Any type of intussusception may recur and, in 8 of the 10 cases, the second intussusception was of the same type as the first. In case 6 (table III), where accurate measurements were made, the apex arose from exactly the same point on both occasions. Apart from the recurrence caused by the inverted appendix stump, no causative lesion was noted in the bowel wall to explain this complication.

Deliberate fixation has not been practised in this series, apart from case 5 in which a cæcocolic intussusception recurred and cæcopexy was done after the second reduction.

This recurrence-rate of 3·8% compares with that of Strang (1959) who recorded 3% recurrences.

Radiology

We do not propose to discuss the interpretation of straight X-rays of the abdomen, which can be of considerable use in some cases, but rather the uses of barium enemas as a means of diagnosis and a means of reduction.

The use of barium enemas for reduction had not been a routine procedure in this hospital until a few years ago. Since then, cases have been referred only sporadically; and these have been dealt with by any member of the radiological staff who happened to be available, whether senior or junior. Hence our results cannot be compared with those from centres where systematic selection was practised, and where reduction was carried out by one interested and experienced radiologist.

Barium enema has been carried out 28 times in this series. In 13 cases, it was used for diagnosis only. The remaining 15 cases, where a definite attempt at reduction was made, were unselected as regards age or length of history; and, in fact, no less than 8 had a history of over thirty-six hours. 5 were reduced, and in 10 reduction was unsuccessful, although in these 10 cases partial reduction was achieved leading to shorter and easier intra-abdominal manipulation. This gives a one-in-three chance of success for this procedure, whereas Hipsley (1926) managed to reduce 62 out of a consecutive 100 cases. Zachary (1955) had a 70% success-rate out of 40 cases with a history of less than twenty-four hours, and 3 out of 12 with longer histories.

Since the period under review in this series, this method has been used much more frequently and with gratifying results. We now advocate that this method be given a trial in those cases where the child is in good general condition and has a short history (cases with a longer history may be included where a chronic or recurring intussusception is suspected). Barium enema is indicated for cases in which anæsthesia is hazardous, because of concomitant disease.

Perforation of the bowel has not been met in this series, and there have been very few recorded cases, except when the head of pressure has been allowed to rise above three feet of barium. Other disadvantages have been stated to be an unwarranted delay in operation (although this may be reduced to a minimum), and the danger of missing an incomplete reduction or an intussusception above the ileocæcal valve.

In spite of these disadvantages, the use of barium enema is a very valuable method in skilled radiological hands. The only real disadvantage met is that a colon loaded with barium adds to the difficulties of resection should this subsequently prove necessary, and retards a smooth convalescence after operation. With careful selection, this disadvantage is minimised.

Mortality

Of the 45 deaths in this series, no less than 32 were within twenty-four hours of operation, and in only 10 of these had resection been necessary. In many cases necropsies were not performed, but we could safely attribute death partly to the effect of surgery on children who were dehydrated and in electrolyte imbalance. 2 were in extremis and died before admission to the ward.

The mortality has been steadily decreasing, and in the last decade of this series, out of 9 deaths, there were none with a history of under twenty-four hours' duration; 5 had a history of forty-eight hours or over.

There are two main factors contributing to this fall in mortality—more modern anæsthesia and a better understanding of fluid and electrolyte balance. We would stress the importance of unhurried and adequate rehydration by intravenous fluid before these cases are submitted to operation.

Summary

The incidence and management of 269 consecutive cases of intussusception in childhood occurring over a thirty-year period are reviewed.

TABLE III—DETAILS OF RECURRENCES

Case	Age (months)	Sex	First intussusception		Second intussusception		
			Date of admission	Operative notes	Time of recurrence	Operative notes	Result
1	10	M	April 1931	Laparotomy on admission. Spontaneous reduction with signs of recent ileoileal intussusception	? 3 days	Died on third day. Recent ileoileal intussusception found at autopsy	D
2	12	M	Dec. 1932	Laparotomy and reduction of unclassified enterocolic intussusception	3 mos.	Laparotomy and reduction of a similar intussusception	A
3	8	M	April 1934	Laparotomy and reduction of unclassified intussusception	5 mos.	Laparotomy and reduction of a similar intussusception	A
4	19	M	Oct. 1935	Laparotomy and reduction of unclassified enterocolic intussusception	25 mos.	Laparotomy and reduction of ileocæcal intussusception	A
5	36	F	Dec. 1939	Laparotomy and reduction of cæcocolic intussusception	7 days	Laparotomy and reduction of recurrent cæcocolic intussusception. Cæcopexy. Died 2 weeks later of gastroenteritis	D
6	11	M	July 1941	Laparotomy and reduction of ileocolic intussusception. Apex 8 in. above ileocæcal valve	6 mos.	Laparotomy and reduction of ileoileal intussusception with apex 8 in. above the ileocæcal valve	A
7	6	F	May 1946	Laparotomy and reduction of ileocæcal intussusception with difficulty	? 9 days	Died on 9th day. Necropsy—acute jejunojejunal intussusception	D
8	14	M	April 1950	Laparotomy and reduction of ileocolic intussusception	12 mos.	Laparotomy and reduction of recurrent ileocolic intussusception	A
9	10	M	Sept. 1956	Laparotomy and reduction of ileocolic intussusception. Appendicectomy	3 days	Laparotomy and reduction of cæcocolic intussusception. Appendix stump forming the apex. Readmitted Jan., 1957, with typical history and abdominal mass. Barium enema—no abnormality. Presumed spontaneous reduction	A
10	4	M	Nov. 1957	Laparotomy and reduction of ileocæcal intussusception	1 mo.	Laparotomy and reduction of recurrent ileocæcal intussusception with difficulty	A

D=died. A=alive.

Factors affecting the mortality-rate are discussed, and a strong plea is made for earlier reference to hospital of any suspicious case.

The mortality-rate fell, from 17·6% in the first decade to 8·9% in the third decade, and we attribute this to better resuscitative and anæsthetic techniques. This fall in mortality has been achieved in spite of an increase in the length of history before reference to hospital.

The ætiology is discussed, and attention drawn to infective and anatomical factors.

The series has been broken down into anatomical types, and their incidence, management, and mortality are described. The high mortality of ileoileal intussusceptions is noted and reasons for this suggested.

Suggestions are made for dealing with the irreducible intussusception. Resection and anastomosis, carried out before prolonged attempts at reduction have produced shock and bowel injury, is the method of choice. Exteriorisation and ileostomy are suggested for the poor-risk case. Other operative procedures are deprecated.

The place for appendicectomy and Meckel's diverticulectomy at the time of reduction is discussed.

The recurrence-rate is reviewed.

The use of barium enema for reduction is advocated in selected early cases with a history of under twenty-four hours and in good general condition.

We should like to thank the many consultants, past and present, under whom these children have been admitted, and the resident staff whose note-keeping has made this review possible. We are particularly grateful to Mr. C. Vincent Patrick, Dr. H. Everley Jones, and Dr. A. P. Booth for helpful advice and criticism.

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ANTIBODIES TO THYROGLOBULIN IN PATIENTS WITH THYROTOXICOSIS TREATED WITH RADIOACTIVE IODINE

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RADIOACTIVE iodine is now an accepted agent in the treatment of thyrotoxicosis in three groups of patients—those over the age of forty, those who have relapsed after partial thyroidectomy, and those who are unsuitable for surgery because of coexistent disease. The only drawback of this treatment, apart from the still undetermined risk of development of thyroid malignancy or leukæmia, is the relatively high incidence of hypothyroidism which results.

According to published series, 5–25% of patients become hypothyroid. In the British Isles, the usual incidence is about 12% one year after treatment (Blomfield et al. 1959, Macgregor 1960). Macgregor (1960) reports that the incidence of hypothyroidism in their patients had risen to 17% three years after treatment and Werner et al. (1957) also recorded the continued development of hypothyroidism for years after treatment. Larrson (1955), however, has shown that thyroid function is at its lowest six to eight weeks after therapy. It would, therefore, appear that the development of hypothyroidism more than a few months after treatment is not directly due to a radiation effect.

The toxic thyroid gland is frequently the site of lymphocytic infiltration; and, after surgical thyroidectomy, there is a relationship between the severity of these histological changes and the incidence of postoperative myxœdema (Whitesell and Black 1949, Greene 1950, 1953). More recently, it has been shown that anti-thyroid antibodies are found in about 60% of patients with untreated thyrotoxicosis (Roitt and Doniach 1958). Smart and Owen (1960) report that they have found these antibodies in 80% of patients with myxœdema following surgery, and suggest that the presence of antibodies in patients with thyrotoxicosis " should probably therefore be accorded clinical significance, at least in deciding the most appropriate form of treatment."

Studies have been reported on only a few patients after treatment with radioactive iodine (Blizzard et al. 1959, Cline et al. 1959). This paper reports the findings in a larger series.

Subjects and Method

Patients with thyrotoxicosis, who had been referred to the isotope department for treatment with ^{131}I, were investigated. Titres of autoantibodies against thyroglobulin were estimated by a modification of the tanned-cell agglutination principle of Boyden (1951), as described by Owen and Smart (1958). In all estimations, known positive and negative sera were included among the controls.

Serum was studied from:

(1) 102 patients with thyrotoxicosis, confirmed by tracer studies, attending for treatment with ^{131}I.

(2) 103 patients attending the follow-up clinic who had been treated with ^{131}I and were subsequently euthyroid. All the patients had been treated at least one year before this investigation.

(3) 58 patients attending the follow-up clinic after treatment with ^{131}I, diagnosed clinically as being hypothyroid—confirmed by tracer studies, blood-cholesterol, electrocardiogram, or basal metabolic rate—who required replacement therapy.

The dosage of ^{131}I used was intended to give 7000–10,000r to the thyroid gland in fourteen days.

Results

The results of clinical follow-up of 67 patients treated with ^{131}I more than six years before this investigation are shown in table I. The incidence of hypothyroidism continues for years after the last dose of ^{131}I. Blomfield et al. (1959) and our own unpublished observations confirm that the development of hypothyroidism cannot be closely related to the size or nature of the thyroid gland, or to any of the physical characteristics usually measured in prescribing treatment with ^{131}I.

Autoantibodies were demonstrated in 53 (52%) of 102 patients with thyrotoxicosis before treatment with ^{131}I, and in 57 (55%) of 103 who were euthyroid for a minimum

TABLE I—THE CONTINUED DEVELOPMENT OF HYPOTHYROIDISM IN 67 PATIENTS TREATED WITH ^{131}I AND FOLLOWED-UP DURING A 6-YEAR PERIOD

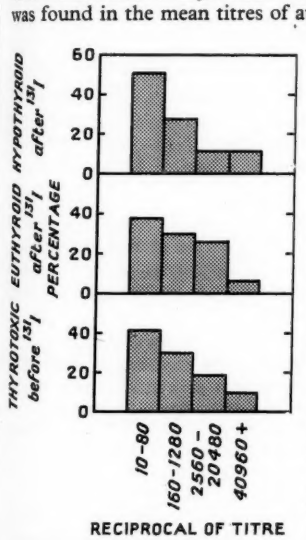
Years since last ^{131}I therapy	Total no. of patients becoming hypothyroid	% of total
0–1	8	12
1–2	10	15
2–3	12	18
3–4	13	19
4–5	17	25
5–6	18	27

TABLE II—PRESENCE OF ANTI-THYROID ANTIBODIES IN SERUM OF PATIENTS BEFORE AND AFTER TREATMENT WITH ^{131}I

—	No. of patients	No. with antibodies	% with antibodies
Pretreatment	102	53	52
Euthyroid after ^{131}I ..	103	57	55
Hypothyroid after ^{131}I	58	45	77

of one year after the last treatment. Of 58 patients with post-therapy hypothyroidism, however, 45 (77%) showed the presence of autoantibodies (table II). This difference is statistically significant ($0{\cdot}001 < P < 0{\cdot}01$). Separation of the hypothyroid patients into two groups—34 who developed hypothyroidism within one year of treatment, and 24 who became hypothyroid more than one year after treatment—shows no difference in the incidence of autoantibodies (76% and 78%).

Roitt and Doniach (1958) reported that in patients with untreated thyrotoxicosis, the titres were nearly always low—i.e., 1/10–1/1520 in approximately 90%, as opposed to the high titres (1/10,240–1/168 million) found in patients with Hashimoto's thyroiditis. No significant difference was found in the mean titres of autoantibody in the three groups in the present series, and they were not significantly higher in the patients developing hypothyroidism (see figure).



Concentration of autoantibodies to thyroglobulin in serum of patients before and after ^{131}I therapy.

Discussion

These results suggest that the development of hypothyroidism following treatment with ^{131}I is associated indirectly with the autoimmunological processes recently described in thyroid disease (Roitt and Doniach 1960). This might be expected in the light of the relationship between histological lymphocytic infiltration of the thyroid gland and the development of myxœdema after surgery (Whitesell and Black 1949, Greene 1950, 1953); the correlation between the presence of anti-thyroid antibodies and the finding of mild Hashimoto-like changes in the thyroid glands of subjects without overt thyroid disease (Goudie et al. 1959); and the recent demonstration that 80% of patients with post-operative myxœdema have demonstrable thyroid autoantibodies (Smart and Owen 1960) as compared with 50–60% of those with untreated thyrotoxicosis.

Hall et al. (1960) have shown that the disposition to develop thyroid autoantibodies may be genetically determined, and sibs of patients with thyroid disease may show the presence of autoantibodies without clinically apparent thyroid disease. Anti-thyroid antibodies are also found in 6–18% of patients without clinical evidence of thyroid disease (Goudie et al. 1959, Hackett et al. 1960).

Complement-fixing autoantibody, present in the sera of about 40% of patients with untreated thyrotoxicosis and directed against an antigen found in the microsome fraction after differential centrifugation of thyrotoxic-gland extract (Roitt and Doniach 1958), was not estimated in the present study. However, Pulvertaft et al. (1959) have shown that the cytotoxic effects of sera from patients with Hashimoto's thyroiditis on thyroid cells in tissue culture appear to be due to a factor other than either the complement-fixing autoantibody or the antibody to thyroglobulin.

In the light of these facts and the generally low titres of autoantibodies in all groups of patients in the present series, it would seem that the antibodies themselves are not directly responsible for the development of hypothyroidism. Their presence may indicate some underlying abnormality, disposing in some cases to ultimate destruction of the thyroid gland. It would, therefore, seem unreasonable at present to withhold such a simple and satisfactory method of treating thyrotoxicosis from patients with a low titre of circulating autoantibodies, particularly as most patients treated are over the age of forty, and, if hypothyroidism should develop, replacement therapy with thyroxine is cheap, easy, and safe.

Patients with Hashimoto's thyroiditis sometimes first attend with thyrotoxicosis (Vaux 1938). The typical hard, horseshoe-shaped goitre of Hashimoto's thyroiditis soon develops and the level of autoantibodies rises greatly (Doniach et al. 1959). It should be easy to distinguish these cases clinically, and by the use of the precipitin test (Doniach and Roitt 1957). This is a simple and relatively insensitive test that is only positive in cases with a high titre of autoantibodies against thyroglobulin. No such case is described in the present series; but it would seem reasonable, if possible, to avoid both surgery and ^{131}I in such patients, because of the risk of causing hypothyroidism. Such patients may, however, be difficult to treat with anti-thyroid drugs because these may cause further enlargement of the goitre.

Summary

Study of the serum of patients before and after treatment of thyrotoxicosis with radioactive iodine showed a significantly higher incidence of circulating anti-thyroid antibodies in those who had developed hypothyroidism. Antibody was found in 52% of patients before treatment, in 55% of patients who were euthyroid at least one year after treatment, and in 77% of patients who had become hypothyroid after treatment. The titre of antibodies was low in most cases in each group.

An autoimmune mechanism may possibly be indirectly associated with the development of hypothyroidism occurring years after treatment with ^{131}I, but the presence of a low titre of anti-thyroid antibodies in patients with thyrotoxicosis is not to be regarded in itself as an indication to withhold treatment with radioactive iodine.

The precipitin reaction should distinguish between hyperthyroid patients and those few patients with early Hashimoto's thyroiditis who present with thyrotoxicosis.

I wish to thank Prof. R. E. Tunbridge for his advice and encouragement, Dr. S. G. Owen for advice on the estimations, and Miss V. Grayson for her assistance with this work.

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PROTEIN-LOSING ENTEROPATHY IN THE SPRUE SYNDROME

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Green and Wollaeger (1958) have criticised the terms "idiopathic steatorrhœa" and "malabsorption syndrome" because they emphasise only one aspect of the malabsorption which affects carbodydrate, protein, vitamins, water, and many substances other than fat. The alternative names of "tropical and non-tropical sprue" or "the sprue syndrome" are preferable

In a survey of non-tropical sprue in the United States, Green and Wollaeger found hypoproteinæmia with the total serum-proteins below 6·0 g. per 100 ml. in 70% of their patients, while the serum-albumin levels were less than 3·5 g. per 100 ml. in 60%. This hypoproteinæmia and the muscle-wasting so often seen in this condition have been attributed to protein malabsorption. The earlier studies of Thaysen (1926), however, showed that small fæcal nitrogen losses, when compared with those of fats, were a diagnostic feature in idiopathic steatorrhœa. Comfort et al. (1953) found that the majority of their patients with sprue had abnormal fæcal nitrogen levels, but could not find any relation between the fæcal fat and fæcal nitrogen excretions. On the other hand, Cooke et al. (1953) found a significant relationship between the fæcal fat and fæcal nitrogen levels in ten cases of idiopathic steatorrhœa.

These observations suggest a significant difference between the metabolism of fat and of protein in the sprue syndrome. Alternatively, the discrepancy could be explained by leakage of protein into the gastrointestinal tract—"exudative enteropathy" or "protein-losing enteropathy" (Gordon 1959, Schwartz and Jarnum 1959). A number of workers have demonstrated this protein-loss in hypertrophic gastritis, Crohn's disease, ulcerative colitis, and other gastrointestinal diseases (Citrin et al. 1957, Steinfield et al. 1957, Gordon 1959, Holman et al. 1959, Jarnum and Schwartz 1960). The discovery by Paulley, in 1954, of atrophic changes in the mucosa of the small intestine of patients with idiopathic steatorrhœa suggests a possible origin for protein-losing enteropathy. Similar histological changes have been shown in patients with cœliac disease by Sakula and Shiner (1957), and in tropical sprue by Butterworth and Perez-Santiago (1958).

Gordon (1959) has described an ingenious technique to demonstrate and to measure this increased intestinal permeability. He used a polyvinylpyrrolidone with a molecular weight about that of albumin. When labelled with radio-iodine this polymer resists the action of digestive juices. After intravenous injection increased intestinal permeability is indicated by the finding of excessive radioactivity in the fæces. Using this technique, Schwartz and Jarnum (1959) demonstrated protein-losing enteropathy in a patient with hypoproteinæmia due to sprue.

The object of this investigation was to determine if protein-losing enteropathy occurred in patients with the sprue syndrome; and to correlate this enteropathy with clinical and histological findings, and with the results of protein-absorption tests.

Patients

Eleven patients were studied. One was a child with cœliac disease. Two adults had symptoms dating back to childhood, and were thought to have adult cœliac disease. Two developed symptoms for the first time while in the tropics, but had relapses after returning to Britain; although initially thought to have tropical sprue, some features suggest that they may be cases of idiopathic steatorrhœa or non-tropical sprue, and belong to the same group as the other six patients in the series. Seven of the eleven patients responded to a gluten-free diet; and may, alternatively, be classed as cases of gluten enteropathy. The term "sprue syndrome" will be used for this whole group of conditions.

The diagnosis was established by the history, the finding of a fæcal fat excretion in excess of 6 g. daily, impaired glucose absorption, and radiological abnormality of the mucosal pattern of the small intestine. Jejunal biopsies in each patient showed atrophic changes in the mucosa.

Methods

All the patients were asked about weight-loss in the months before admission. Routine estimations of the hæmoglobin, serum-proteins, and albumin levels were made. Fæcal fat was calculated as the mean daily excretion during a 4-day collection, while receiving a 70 g. fat diet.

Jejunal Biopsies

Jejunal biopsies were obtained by the capsule method of Crosby and Kugler (1957). Biopsy specimens varied in size from 7 to 15 mm. in diameter. After careful orientation, they were fixed in formal-saline and embedded in wax. Accurately cut perpendicular sections were stained with hæmatoxylin and eosin. Histological changes in the epithelium, the size and shape of the villi, and the amount of cellular infiltration were assessed, without knowledge of the clinical findings.

Radio-iodine-labelled Albumin

Albumin labelled with radio-iodine (^{131}I-albumin) was used to assess the efficiency of absorption of ingested protein. The method was that described by Chinn et al. (1953). ^{131}I-albumin was prepared by the method of Veall et al. (1955). The dose, containing approximately 20 μC of radioactivity, was given to the fasting patient with a carrier of gelatine, 0·5 g. per kg. body-weight. For the 24 hours before the test, and for the succeeding 4 days, potassium iodide 60 mg. three times daily was given to prevent thyroid uptake of radio-iodine. All the fæces passed in the 4 days after the dose were collected, and the radioactivity assayed by comparison with a known fraction of the dose administered. Radioactivity was measured in a multiple component Geiger-Müller ring-counter connected to an 'Ekco Autoscaler'. Results were expressed as the percentage of the administered dose excreted in the stools during the 4-day collection. Normal excretion was less than 5%.

Radio-iodine-labelled Polyvinylpyrrolidone

This material was obtained from the United States, through the courtesy of Dr. Robert S. Gordon.

Before injection, the solution was dialysed to exclude contamination by unbound radioactive iodine or by polymer of low molecular weight. After being autoclaved, a dose of about 10 μC was given intravenously. A standard was prepared using a

DR. BLAGG: REFERENCES—*continued*

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CLINICAL DETAILS OF PATIENTS, RESULTS OF ISOTOPE STUDIES, AND HISTOLOGICAL GRADINGS OF BIOPSY SPECIMENS

—	Case no.										
	1	2	3	4	5	6	7	8	9	10	11
Sex	F	F	M	F	M	F	M	F	F	F	M
Age (years)	65	46	44	29	58	50	49	18	1 10/12	34	58
Symptoms	D, T	T	D, H	D	D, B	D, S	D	S	S	D	D, B
Weight-loss (kg.)	6·0	3·2	9·7	6·2	6·4	14·5	6·0	38·7*	8·7*	3·7	8·2
Hæmoglobin (g. per 100 ml.)	10·6	12·1	10·3	9·3	11·2	9·8	13·1	13·0	8·3	8·3	14·5
Type of anæmia	M	M	M	M	M	M	Nil	F	F	F	M
Serum-albumin (g. per 100 ml.)	4·7	3·5	4·0	3·8	4·0	3·6	4·9	4·8	5·6	2·7	3·0
Fæcal fat (g. per 24 hours)	21·3	29·0	16·4	20·7	30·0	10·0	25·0	13·3	18·0	10·4	9·4% †
Biopsy:											
Epithelium	2	3	3	3	3	0	0	2–3	3	3	3
Villi	1	3	3	3	3	1	1	3	3	3	3
Cellular infiltration	2	2	2	2	3	1	3	3	2	3	3
Fæcal ^{131}I-albumin (%)	1·3	6·3	0·6	1·2	14·9	0·3	1·6	0·9	3·8	1·8	5·5
Fæcal ^{131}I-P.V.P. (%)	3·6	1·4	2·1	0·8	3·0	0·3	0·7	1·0	6·7	0·8 1·4	0·9
Gluten-sensitivity	Yes	?	Yes	?	Yes	?	Yes	Yes	Yes	?	Yes
Final diagnosis	I.S.	I.S.	?S	I.S.	I.S.	A	I.S.	C	C	A	?A

T = tetany. D = diarrhœa. H = hæmorrhage. S = stunting. B = bone pain. M = megaloblastic. F = iron-deficient. C = cœliac. A = adult cœliac S = tropical sprue. I.S. = idiopathic steatorrhœa. * = actual body-weight. † = ^{131}I-fat excretion. ^{131}I-P.V.P. = radio-iodine-labelled polyvinylpyrrolidone.

known fraction of the dose administered. Fæces were collected for the next 4 days and the radioactivity assayed in the same way as for the ^{131}I-albumin. The results were expressed as the percentage of the administered dose found in the fæcal collection. Gordon (1959) states that the fæcal excretion of radio-iodine-labelled polyvinylpyrrolidone (^{131}I-P.V.P.) in forty-one normal subjects was less than 1·5% of the dose. In ten normal subjects examined by me, the fæcal excretion was found to be less than 1%.

A maximum dose of 1 μC was used for each of the two tests for the one child in the series. The stools were homogenised, and aliquots counted in a thallium-activated sodium-iodide crystal-well-type scintillation counter connected to an Ekco autoscaler.

Care was taken to exclude urinary contamination of the fæcal collections.

Results

The clinical details of the eleven patients, the results of the isotope studies, and the histological gradings are summarised in the table.

Jejunal Biopsies

The histological changes in the intestinal mucosa were assessed under three headings:

1. The orderliness and cellular height of the mucosal epithelium.
2. The height, shape, width, and fusion of the villi, and the depth of the crypts.
3. The total thickness of the mucosa glandular layer and the degree of cellular infiltration.

Changes were graded from 0 to 3 (0=normal, 3=severe). The biopsy specimens were graded without knowledge of the clinical details.

In patients 2 and 7, the biopsies were repeated after an interval of 2 and 6 months respectively, and no significant changes were observed.

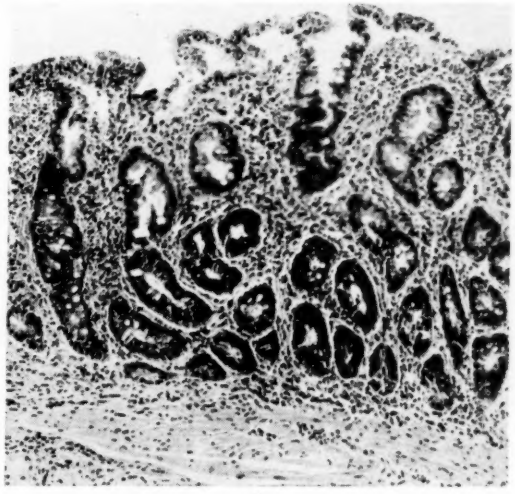
Radio-iodine-labelled Albumin Absorption

Three patients excreted an abnormal percentage of the administered dose in the fæcal collection: case 2, 6·3%; case 5, 14·9%; and case 11, 5·5%. Each had considerable steatorrhœa at the time of testing and their fæcal fat excretions were the highest in the series.

The fæcal losses of ^{131}I-albumin, however, were not closely related to the severity of the disease or the steatorrhœa when the whole group was considered, nor was there a relationship between the level of the total serum-proteins or serum-albumin and the fæcal excretion of radioactivity.

Radio-iodine-labelled Polyvinylpyrrolidone

Four of the eleven subjects excreted more than 1·5% of the administered dose in the 4-day fæcal collection. (case 1, 3·6%; case 3, 2·1%; case 5, 3·0%; and case 9, 6·7%).



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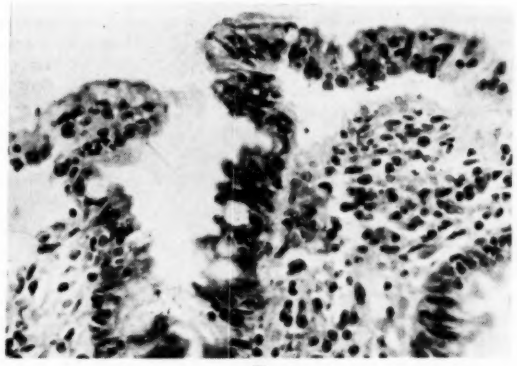


B

Fig. 1, A and B—Jejunal biopsy (case 5), before gluten-free diet. (A×30, B×120.)

The fæcal excretion of the tracer could not be related to the clinical severity of the disease, nor to the weight-loss in the months preceding the investigation.

There was no relationship between the excretion of ^{131}I-P.V.P. and the level of the serum-albumin, the total serum-proteins, or the fæcal fat excretion. Similarly there was no correlation between the fæcal losses of ^{131}I-albumin and ^{131}I-P.V.P.

Only case 5 had a high elimination of both tracer substances; despite this, the serum-albumin and total proteins remained just below the normal range. His steatorrhœa was severe, and he was the only patient in the series with bone pain.

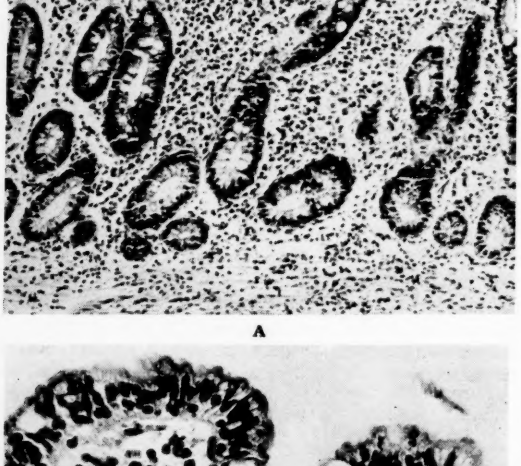
Three of the four patients excreting an abnormal percentage of ^{131}I-P.V.P. showed severe abnormality of the jejunal mucosa, and each responded satisfactorily to a gluten-free diet.

Illustrative Case-record

A man, aged 58 (case 5). In 1952, he had diarrhœa with pale frothy stools, and soreness of the tongue. There was no past history of bowel disturbance or of residence in the tropics. Investigation at that time showed steatorrhœa and a megaloblastic anœmia. Non-tropical sprue was diagnosed and treatment was begun with folic acid and a low-fat diet. Bouts of intermittent diarrhœa persisted until 1959, when he attended here with bone pain and a recurrence of diarrhoea, having lost 14 lb. (6·3 kg.) in the preceding year.

There was no abnormality, other than weight-loss and bone-tenderness. He was found to have a mild macrocytic anæmia with hæmoglobin 12 g. per 100 ml. (81%). Serum-calcium 3·6 mEq. per litre, serum-phosphate 3·1 mg. per 100 ml. serum-proteins 5·7 g., albumin 4·0 g., globulin 1·7 g. The glucose-absorption curve was flat, and the fæcal fat excretion 30 g. daily. Radiologically, the small intestine had an abnormal mucosal pattern. A jejunal biopsy confirmed that there was severe villous atrophy (fig. 1). The fæcal excretion of ^{131}I-albumin was raised, 14·9% of the administered dose being lost in the 4-day collection. The fæcal loss of ^{131}I-P.V.P. was also high, 3·0% of the dose being found in the 4-day period.

The response to a gluten-free diet was dramatic; within 2 weeks, the patient was passing formed stools for the first time in 7 years.



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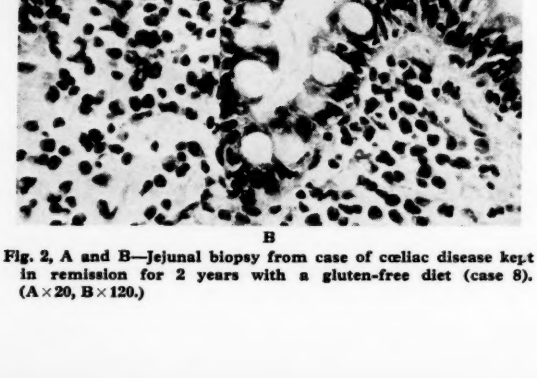

B

Fig. 2, A and B—Jejunal biopsy from case of cœliac disease kept in remission for 2 years with a gluten-free diet (case 8). (A×20, B×120.)

Discussion

This investigation shows that protein-losing enteropathy does occur in some patients suffering from the sprue syndrome. The present study, however, fails to show any relationship between the level of the serum-albumin and the fæcal losses of the ^{131}I-P.V.P., such as was found by Gordon (1959), in his studies of patients with idiopathic hypercatabolic hypoproteinæmia.

The one patient (case 10) in the present series with severe hypoproteinæmia on two occasions had losses of ^{131}I-P.V.P. within the normal range.

The lack of correlation between the appearances of the jejunal mucosa and the losses of ^{131}I-P.V.P. suggest that these histological changes are not responsible for the increased intestinal permeability. Culver et al. (1959) report that they were unable to find any constant relation between the severity of malabsorption and the histological changes seen on jejunal biopsy from patients with sprue. These observations, and the finding of severe grades of mucosal atrophy in cœliac disease after long-lasting remission on a gluten-free diet (fig. 2), indicate that the factor responsible for the increased permeability and malabsorption is not the histologically visible lesion but is possibly an enzymal defect of the mucosal cell.

The lack of correlation between the absorption of ^{131}I-albumin and the fæcal losses of ^{131}I-P.V.P. seems to indicate that the processes of protein absorption and protein-losing enteropathy are independent.

This study suggests that the protein disturbances of sprue are complex, and not solely attributable to protein malabsorption, or to increased intestinal permeability or even to a combination of these two processes.

Summary

Eleven patients with the sprue syndrome have been investigated with radioactive-isotope tracers to detect the presence of protein malabsorption and protein-losing enteropathy.

Protein malabsorption was detected in three, and protein-losing enteropathy in four. No correlation could be found between these defects of protein metabolism and the clinical state, nor with the level of serum-proteins, or the histological changes in the mucosa of the small intestine.

My thanks are due to the physicians of Charing Cross Hospital, and to Dr. C. C. Booth of the department of medicine, Postgraduate Medical School, for allowing me to investigate their cases; also to the sisters and nurses of these hospitals for their cooperation.

References at foot of next column

DANGEROUS GROUP-O BLOOD

A SIMPLIFIED TEST

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SOME group-O bloods are regarded as unsuitable for emergency transfusion to recipients of other groups because their plasma contains anti-A or anti-B antibodies in critically high titre. Gardner and Tovey (1954) have described a screening test for detecting anti-A and anti-B hæmolysins and immune agglutinins, and it is generally agreed that a separate test for high-titre saline agglutinins is unnecessary, since they are almost always associated with hæmolysins (Medical Research Council 1958). The screening test recommended has the disadvantage that about 20% of group-O bloods show hæmolysins, hence there may be difficulty in supplying enough blood for emergency use. Since, however, there is evidence that only those bloods which contain a considerable amount of hæmolysin are dangerous, it has been advised that samples giving a positive result in the screening test should be further tested and labelled as unsuitable for transfusion to recipients other than O only if the hæmolysins are present at a titre greater than 1/8 (Medical Research Council 1958). In a busy laboratory such titrations may appreciably increase the volume of work, as well as introducing the need for a lysin-free complement. Winstanley et al. (1957) have shown that sera containing anti-A hæmolysins and immune agglutinins agglutinate pig red cells containing the A^P antigen, and during investigations of this reaction about one-third of these sera were found also to hæmolyse the group-A pig cells (Lockyer 1959). We undertook an investigation therefore to determine whether the test for dangerous group-O donors could be simplified by using group-A^P cells instead of human group A_1.

Materials

Samples of clotted and citrated blood (approximately 20 ml. in 6 ml. of acid-citrate-dextrose (A.C.D.) were collected weekly from each of 10 pigs slaughtered at a local abattoir, and stored at 4°C until required.

Grouping of pig red cells.—The pig red cells from the citrated samples were washed three times with 1·5% saline to minimise autohæmolysis (Lockyer 1959), and papainised by incubating the washed packed cells at 20°C for 5 minutes with an equal volume of Löw's papain. The cells were then washed once, diluted to an approximate 10% suspension in 1·5% saline, and incubated with an equal volume of pig anti-A serum in $3 \times {}^3/_8$ in. tubes for 1 hour at 20°C. About one-third of the pig samples grouped as A^P by this technique, some weakly, some strongly. The cell suspensions showing the strongest reactions were selected as the A^P test cells.

Selection of pig anti-A sera.—One volume of a 10% suspension of washed red cells in 1·5% saline from each of the citrated samples was incubated for 1 hour at room temperature with one volume of serum from each of the 10 clotted samples. Any serum agglutinating some of the pig-cell suspensions was then known to have come from a group-O pig and to contain anti-A^P agglutinins. The strongest reactors were stored at −20°C for grouping subsequent samples of pig cells.

Group-O sera.—The sera investigated were those from routine blood-donor sessions and were examined for hæmolysins within 24 hours of collection. Some sera were further tested after storage as whole clotted blood for 48–72 hours at 4°C.

Complement.—Fresh group-O serum, proved free of hæmolysins and low in anti-A and anti-B titre, was used. Complement activity was tested by adding the serum to an inactivated serum known to contain anti-A hæmolysins; group A_1 cells were then added to test for reactivation. Sera found to be rich in complement and free of hæmolysins were freeze-dried, stored, and reconstituted with distilled water immediately before use.

Methods

Sera from group-O donors, bled at routine blood-donor sessions, were screened for hæmolysins by the method described by Gardner and Tovey (1954). Those showing a positive result at 37°C were further tested at a dilution of 1/8 by the method recommended in the M.R.C. memorandum (Medical Research Council 1958).

All sera hæmolysing human A_1 or B cells at 37°C were further tested for anti-A^P hæmolysins by incubating equal volumes of the serum and a 10% suspension of non-papainised A^P cells in 1·5% saline in $3 \times {}^3/_8$ in. tubes for 1 hour: a suspension of group-O^P cells was similarly tested as a control. To begin with these tests were carried out at 37°C, but it was found that the A^P and O^P cells showed non-specific hæmolysis at this temperature. Hæmolysis of A^P cells was specific at room temperature (about 20°C), and the routine tests for anti-A^P hæmolysins were therefore carried out at this temperature. When the sera were tested within 48 hours of collection, the addition of complement was unnecessary. An equal volume of reconstituted freeze-dried serum containing complement was added to sera tested more than 48 hours after collection. The pig cells collected into A.C.D. remained satisfactory as test cells for at least 7 days when stored at 4°C.

TABLE I—INVESTIGATION OF SERA FOR HÆMOLYSINS

Total group-O sera examined	2500
Number hæmolysing human A_1 cells at 37°C	450 (18%)
Number hæmolysing A_1 cells at a titre of 1/8	90 (3·6%)
Number hæmolysing A^P cells at room temperature	105 (4·2%)

Results

The results of examining 2500 group-O sera for hæmolysins are summarised in table I. Had Gardner and Tovey's screening test for hæmolysins been used, 450, or 18%, of the bloods under test would have been labelled as " dangerous ". Only 90 of these, in fact, contained hæmolysins for human A or B cells at a titre of 1/8, and the serum from each of these samples hæmolysed pig group-A cells at room-temperature. A further 15 sera also hæmolysed the A^P cells, so that if pig group-A cells were used as a routine, 105 of the 2500 group-O bloods, or about 4%, would be labelled as " dangerous ". These

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15 sera were further tested at 37°C and found to contain hæmolysins for human A_1 cells at a titre of 1/4–1/6.

These findings show that by using A^P cells, the hæmolysin test for dangerous universal donors is considerably simplified, and that a single-tube test at room temperature should result in the detection of all potentially dangerous group-O bloods. 182 of the 450 sera which contained hæmolysins at 37°C hæmolysed human group-A_1 cells at room temperature, and included in these 182 sera are the 90 which contained hæmolysins at a titre of 1/8. When A^P cells are not available, a hæmolysin test at room temperature using human A_1 cells should also prove adequate, but nearly twice as many group-O bloods will then be labelled as potentially dangerous.

None of the 2500 group-O bloods tested contained anti-B hæmolysins only. When these were present, the sera contained anti-A hæmolysins also. A test using A^P cells only is, therefore, probably sufficient, but Gardner and Tovey (1954) found 2 of 1960 random group-O sera with anti-B hæmolysins only. In neither instance was the titre of the hæmolysin recorded, but until it has been established that anti-B hæmolysins are never present in critical titre independent of anti-A, it is a simple practical measure to use a mixture of equal volumes of a 10% suspension of pig group-A cells and human group-B cells in 1·5% saline as the test cells. Of the 2500 group-O bloods tested 18 hæmolysed group-B cells at room temperature. In 8 instances the anti-B hæmolysin was associated with a high-titre anti-A_1 hæmolysin, so that using a mixture of group-B human cells and A^P cells should result in fewer than 1 in 200 additional group-O bloods being labelled as " dangerous ".

A further 1000 group-O sera were examined to check whether high-titre saline agglutinins and significant immune anti-A antibodies are found only in sera containing anti-A^P hæmolysins. Table II shows that all of the sera containing saline anti-A agglutinins at a titre of 1/500 or immune anti-A antibodies hæmolysed the A^P cells. One may conclude that a screening test for anti-A^P hæmolysins will therefore also protect the recipient against the transfusion of blood containing immune anti-A or saline agglutinins in high titre.

TABLE II—COMPARATIVE INVESTIGATION OF 1000 SERA FOR HIGH-TITRE SALINE AGGLUTININS, IMMUNE ANTI-A ANTIBODIES, AND ANTI-A^P HÆMOLYSINS

	Titre of saline agglutinins		
	1/200	1/500	1/1000
Number showing high-titre saline agglutinins	71	15	5
Number showing immune anti-A	44	15	5
Number hæmolysing A^P cells	50	15	5

To determine whether complement should be added as a routine, 312 group-O sera which did not hæmolyse A_1 cells at 37°C were further tested after adding one volume of freeze-dried human complement:

2 of the sera now showed hæmolysins, but only at a titre of 1/2, demonstrating that, when the samples are fresh, supplementary complement is not required. 15 of the sera containing anti-A^P hæmolysins were retested after storage at 4°C for 48 hours and 72 hours without the addition of complement. All 15 stored for 48 hours hæmolysed A^P cells at room temperature; but, after 72 hours' storage, the hæmolytic activity of 10 of the 15 sera was considerably weakened, although still detectable.

It is advisable that complement should therefore be added if the hæmolysin-screening test is not carried out within 48 hours of blood-donation.

Summary

A simplified test for potentially dangerous group-O blood is described. The test requires the incubation at room temperature of a 10% suspension of a mixture of group-A pig cells and human group-B cells, using 1·5% saline, with an equal volume of the fresh group-O serum.

Sera containing anti-A or anti-B saline agglutinins, immune agglutinins, or hæmolysins in critically high titre, hæmolyse the test cells after incubation for 1 hour at this temperature. By this technique, about 4% of group-O bloods are labelled as potentially dangerous.

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RENAL BIOPSY WITH MODIFIED MENGHINI NEEDLE

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IT is now nine years since acceptable methods for needle biopsy of the kidney were first introduced (Iversen and Brun 1951, Kark and Muehrcke 1954, Muehrcke et al. 1955), and very few serious complications have been reported. One recent series (Kark et al. 1958) comprises 500 biopsies without fatality; blood-transfusion was required twice, but there were no complications requiring surgery. The method used by Kark and his coworkers—biopsy in the prone position with the Franklin Vim-Silverman needle—has largely superseded the older techniques, and in the hands of its originators it gave an acceptable success-rate—80% of all attempts yielded sufficient biopsy material for diagnosis. Biopsy specimens reflect the histological picture of the whole kidney in a high proportion of cases (Kellow et al. 1959). Even now, however, this diagnostic aid is available in only a few British hospitals. The problems that have limited its application may be appreciated from the full review of the method by Kark et al. (1958), and have been underlined by personal experience and by discussion with a number of other workers in this country. They are:

(1) *The kidney is not an easy target.*—7% of the biopsy attempts in Kark's series yielded no renal tissue, and the initial attempts of less-experienced operators (including myself) using their technique have had a much higher failure-rate. This is doubly disturbing since a needle which misses the kidney is in danger of hitting small bowel or colon which may be less mobile than usual owing to compression of the abdomen over a sandbag. None of Kark's patients showed unequivocal signs of bowel perforation, but this remains a real hazard to anyone who cannot locate the kidney. No details are given in Kark's paper about the number of times the biopsy needle was inserted before the procedure was abandoned, but some operators allow themselves two or three attempts; few could resist the temptation to explore a little deeper each time.

(2) *The specimens obtained are not always histologically adequate.*—The histologist is usually more interested in the cortex than in the medulla; so Kark and his colleagues used the number of glomeruli in serial sections through the biopsy specimen as a criterion of adequacy. Five or more glomeruli were accepted as a reasonable sample; and, on this basis, 20% of

attempts yielded inadequate tissue. A more exacting histologist who demanded ten glomeruli per single section would have classified more than half of the biopsy attempts as unsuccessful. Some biopsies taken with the Vim-Silverman needle contain very little cortex, presumably because the trocar and sheath are inserted a short distance into the kidney before the biopsy is taken. In a pathological kidney, with a cortex only a few millimetres thick, the specimen may consist largely of medulla.

(3) *Although dangerous complications are rare, troublesome ones are fairly common.*—Of Kark's patients, 9·8% suffered from one of four unpleasant side-effects—gross or prolonged hæmaturia, renal colic, perirenal hæmatoma, or renal infection. The discomfort following renal biopsy is one of the factors limiting its application in the nephrotic syndrome of children.

These drawbacks of the standard method of renal biopsy are far outweighed by its usefulness, but they leave considerable scope for improvement in the technique. A modification, which I described here, has proved more satisfactory in my hands than the original method of Kark and Muehrcke.

Present Method

The usual preliminary tests of platelet-count, prothrombin-time, clotting-time, bleeding-time, and blood-group are done. Premedication is given to some adults; all children are heavily sedated with a "cocktail" of pethidine, promethazine, and promazine which has proved highly successful in allaying anxiety and discomfort while preserving cooperation. The patient lies prone with a firm pillow supporting the abdomen. I do not believe that this immobilises the kidney appreciably, but it does flatten the lumbar curvature and improve access.

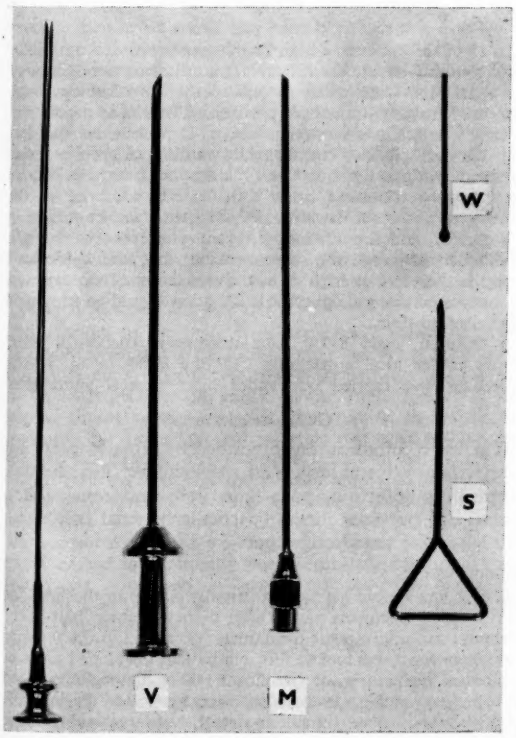

Fig. 1—Menghini-type biopsy needle (M) compared with standard Vim-Silverman needle (V).
Also shown are wire stop from Menghini needle (W) and stilette used for puncturing the skin (S).

Biopsy Needle

The needle (fig. 1) is a lengthened version of the liver-biopsy needle described by Menghini (1958) which I had previously found most satisfactory for its original purpose. Menghini mentioned that his needle was suitable for renal biopsy.

It has been manufactured for us in this country, and is supplied with a slightly bevelled pointed end, which differs from that used by Menghini for liver biopsy.* I have found that the needle performs better, in vitro and in vivo, if it is further sharpened with an inside bevel, by means of a fine-pointed stone on a dental drill, and smoothed on an oil-stone (fig. 2). The needle relies entirely on the sharpness of its edge to cut a biopsy specimen since it is not rotated during the procedure. A 10 cm. needle has proved satisfactory for adults, and a 7 cm. needle (liver-biopsy size) for small children. We have used needles of 1·6 mm. outside diameter and about 1·3 mm. inside diameter which cut biopsies of about the same diameter as those obtained with the standard Franklin Vim-Silverman needle; because of its very thin walls, the Menghini needle has a smaller outer diameter than the sheath of the Vim-Silverman (fig. 1), and therefore makes a smaller hole in the surface of the kidney.

Fig. 2—Enlarged view of point of Menghini biopsy needle to illustrate method of sharpening.

This needle was chosen because of its better performance in preliminary tests on isolated kidney. The Vim-Silverman needle sometimes failed, in spite of transient hæmaturia which showed that the kidney had been penetrated. Various biopsy needles were therefore tested on isolated (necropsy) material under direct vision. Individual Vim-Silverman needles differed in their performance, some giving as few as 50% successful "biopsies" when inserted directly into the kidney. All Menghini needles, sharpened as described, had a "success-rate" of more than 90% when similarly tested.

Any needle for renal biopsy should be tested on isolated material before being used on patients.

Locating the Kidney

Muehrcke et al. (1955) marked on the skin the position of the kidney with the aid of a preliminary intravenous pyelogram taken with patients prone. When using their method, I compared the surface marking with the actual position of the kidney shown by a second pyelogram taken at the time of biopsy and viewed through the image-intensifier. In some patients there was considerable discrepancy—the original estimate being too low in every case. Presumably these errors are due to slight differences in the position of the patient; the phase of respiration is particularly difficult to standardise.

Considerable errors are also introduced by the magnification and distortion of the radiograph. Accuracy could be improved by meticulous standardisation of technique on all occasions, but many of the errors may be eliminated more simply by performing intravenous pyelography at the time of the biopsy.

Ten minutes after injection of the contrast medium, a wire grid is placed on the patient's back over the expected position of the lower half of the kidney from which the biopsy is to be taken. The X-ray tube is centred on the middle of this grid, and films are taken in full inspiration and full expiration. From the films, the appropriate square of the grid is chosen as the surface marking for the biopsy site, and the phase of respiration

* The modified Menghini needle can be obtained from Charles Thackray & Co., Ltd., Park Street, Leeds.

is selected. In some patients the kidney moves several centimetres between full inspiration and full expiration, and it is therefore unwise to aim at a point close to the edge of the kidney.

All the failures and most of the complications have arisen during attempts to locate the lower pole of the kidney. Presumably this means that, even with these precautions, the surface marking of the renal outline is only approximate; attempted " biopsies " on cadavera have convinced me that the lower pole is a difficult target. Possibly one pole of the kidney can be pushed away by the biopsy needle. The site now selected for biopsy is a point about 1 inch medial to the outer edge of the kidney, between the lower and middle calyces.

Determination of the distance of the kidney from the skin has proved more difficult. After injection of local anæsthetic into the skin and lumbar muscles, a fine-bore (21 S.W.G.) exploring needle is passed vertically downwards from the surface marking until a swinging movement, related to respiration, indicates that it has entered the kidney, as described in Muehrcke's (1955) paper. The value of this sign is still uncertain, since a very similar respiratory oscillation is produced when the needle is in perinephric fat below the lower pole. This observation has been made several times with the aid of the image-intensifier. The sensation of entering the kidney substance has been noted in only about two-thirds of the patients. The most useful sign has been a pulsation, in time with the heartbeat, transmitted to the needle when it enters the kidney (Kark et al. 1958). A more certain method of determining the depth of the kidney from the surface is needed, and I am experimenting with nephrotomography at the time of biopsy as a possible alternative. Radiographs in two planes were utilised by Iversen and Brun (1951), but the distance of the kidney from the lateral film makes accurate measurement difficult.

Aspiration of Biopsy

The needle is used as in liver biopsy (Menghini 1958). A tiny incision is made in the skin and the needle, attached to a syringe, is inserted to a depth of about 1 cm. A few drops of saline are blown through the needle to clear it of fat, &c., and it is then inserted into the kidney and withdrawn in one rapid movement, with suction applied to the syringe throughout. Suction must be maintained during insertion of the needle, and this requires a little practice which is best obtained on the cadaver. Either a guard, as fitted to a sternal puncture needle, or the finger, can be used, to prevent too deep insertion of the biopsy needle. The specimen remains in the needle, and is blown out into preservative. If no biopsy is obtained, a second insertion of the needle is permissible, and has been required in about one-third of the biopsy attempts.

Results

This procedure has been tried 50 times, and 48 specimens of renal tissue have been obtained. The specimens were handled by the routine histological laboratory, and counts of the number of glomeruli in a single section through each specimen have been taken from the original slides. The results are shown in the table, and are compared with figures derived from fig. 2 in the article by Kark et al. (1958). Where several sections were cut for different stains, the highest individual count is quoted. Better results could be obtained by careful sectioning along the centre of the biopsy specimen and by serial sectioning, but these have not been carried out routinely.

NUMBER OF GLOMERULI IN SINGLE SECTIONS THROUGH BIOPSY SPECIMENS

Number of glomeruli per section	Number of specimens in this group	Percentage of all attempts	Corresponding percentage in series of Kark et al. (1958)
0 (a) No renal tissue..	2	4	7
0 (b) Renal tissue but no glomeruli ..	0	0	5
1–4	2	4	15
5–9	6	12	30
10–14	8	16	22
15–19	8	16	8
20–24	14	28	7
Over 24..	10	20	5
5 or more	46	92	73
10 or more	40	80	42

Kark's criterion of adequacy cannot therefore be applied to the present material; but, using a stricter requirement of five glomeruli per single section, an acceptable biopsy was obtained in 46 of 50 attempts (92%). The average number of glomeruli per slide was twenty-one, which is about twice the figure for Kark's series, suggesting that specimens taken by the new technique contain more renal cortex.

There is no simple measure of the amount of renal medulla on a slide, and Kark et al. gave no indication of the amount in their specimens. Using a rough rule-of-thumb classification of " adequate " or " inadequate ", it was estimated that 11 specimens contained too little medulla; my impression is that a higher proportion of biopsies taken with the Vim-Silverman needle contain adequate medulla, but there is insufficient material for a fair comparison. In any case, present histological opinion appears to be that in making a diagnosis the amount of cortex is much more important than the amount of medulla.

In 12 of the patients, a high blood-urea precluded the use of pyelography to locate the kidney. Plain films or tomograms of the renal area were taken to ensure that two kidneys were present in roughly the normal position. The biopsy needle was inserted vertically downwards about 1 cm. below the last palpable right rib, 6–7 cm. from the midline. A specimen was obtained without difficulty in 11 cases; and, in the 12th, a specimen was obtained on a third insertion of the needle immediately below the twelfth rib. Diagnosis was important in this patient, and the making of several attempts was thought justifiable. Although the success-rate in the " blind-biopsy " group is therefore as high as in the remainder of the series, I am convinced that radiographic localisation should be employed whenever possible.

5 children, aged 8–14, have undergone successful renal biopsy under local anæsthesia. In one child, aged 7, the procedure was carried out under brief general anæsthesia.

Complications

The main complications described by other workers are hæmorrhage (hæmaturia and perinephric hæmatoma), perinephric infection, pain (loin pain and renal colic), flare-up of previous illness (particularly renal infection), and biopsy of the wrong organ.

Hæmorrhage

There was visible hæmaturia (usually slight) in the first one or two urine specimens passed after biopsy in about half of the patients; and microscopic hæmaturia was found in the remainder whenever it was looked for. No patient developed gross or prolonged hæmaturia, or significant fall in hæmoglobin level, after biopsy; and no transfusions were required. Perinephric hæmorrhage is more difficult to detect, but large hæmatomata are said to produce a shadow on straight X-rays or on tomograms of the renal area (Kark et al. 1958). Plain films were taken in every patient who had significant pain after biopsy, and tomograms were taken in 2; no hæmatomata were detected.

Perinephric Infection

1 patient suffered a complication which was attributed to perinephric infection. He was a child, aged 7, with severe nephrotic syndrome and moderate azotæmia due to type-I nephritis, and underwent right renal biopsy without incident. Culture of the washings from the biopsy needle was sterile, but coliform organisms were found in the first midstream urine after biopsy. He was given a seven-day course of sulphonamides to which the organisms were sensitive; at the same time (forty-eight hours after biopsy) prednisone therapy was begun. There was no improvement in the nephrotic syndrome, but there were no complaints referable to the biopsy. Two weeks later he suddenly complained of pain in the right loin, and became extremely tender there and on the right side of the abdomen. His temperature rose to 100°F, and a leucocytosis of 18,000 per c.mm. developed over the next twenty-four hours. Urine culture was sterile. He was treated with erythromycin and furaltadone, and made a satisfactory recovery.

Pain

Slight aching in the loin, usually at the biopsy site, and commonly related to movement, was often present in the first twenty-four hours. 5 patients had more severe pain during or after biopsy. 1 adult complained of loin discomfort for three days after biopsy, and another had fairly severe pain immediately after the procedure, which gradually subsided over the next four days. Both were tender over the affected kidney and, although tomograms showed no evidence of large extravasation, it was thought that a small subcapsular hæmatoma might be responsible for the pain. Kark et al. (1958) commented that relatively small subcapsular and perinephric hæmatoma could cause quite severe discomfort.

A child, with relapsing nephritis and probable Henoch's purpura, had discomfort in the loin in the first twenty-four hours after biopsy; and, five days later, a further attack of loin pain associated with slight hæmaturia. In view of the time interval, the second attack may have been due to a flare-up of the illness following biopsy.

A child with nephrotic syndrome and azotæmia, in whom biopsy material was obtained with difficulty, had pain in the right loin and iliac fossa for two days afterwards. There was guarding and rebound tenderness over the right side of the abdomen, but no fever or leucocytosis, and the condition cleared up spontaneously. It was thought that, on the initial insertion, the biopsy needle had passed below the lower pole of the kidney and may have produced a small amount of peritoneal bleeding. There was no fall in hæmoglobin level.

A 5th patient suffered some loin pain in association with urinary infection after biopsy.

Flare-up of Original Disease

In addition to the child with nephritis 2 patients had an obvious exacerbation of their illness after biopsy. A child of 14 with nephrotic syndrome was treated by bed rest and diet for one week after admission, and proteinuria fell from 15 g. per litre to almost zero. The day after biopsy there was no hæmaturia but urinary protein excretion rose again to 12 g. per litre. It fell back to zero during a course of corticotrophin (A.C.T.H.) started forty-eight hours after biopsy. The specimen showed fairly severe thickening of basement membranes (type-II nephritis).

A woman of 45 with a history of recurrent loin pain and frequency had intermittently positive urinary cultures. After biopsy, her urine became heavily infected with organisms similar to those in her last positive culture, and she developed typical symptoms of a urinary infection. This cleared up with antibiotic therapy and she has remained well since.

Biopsy of Wrong Organ

Accidental biopsy of some organ other than the kidney is a not uncommon error but one which did not occur in the present series. One biopsy of kidney also contained a tiny fragment of duodenum, and another biopsy included a portion of myocalyx muscle. Neither patient appeared to suffer any harm, which is interesting in view of Kark's conclusion that biopsy of the myocalyx might be responsible for pain at the time of biopsy. This patient was carefully questioned; but had felt no pain whatever after the procedure.

Comparison of the incidence of complications in different series is of questionable value since so much depends on the observer's opinion of, for instance, where mild discomfort ends and pain begins. However, the incidence of uncomfortable complications in this small series (12%) is reasonably close to that in Kark's much larger one (10%).

Summary

A technique of renal biopsy is described which employs a modified Menghini needle and in which the position of the kidney is determined, when possible, by pyelography at the time of biopsy. The results of 50 biopsy attempts are reported.

In this series the success-rate is higher than with the standard method, using the Vim-Silverman needle. The incidence of complications is similar.

The specimens obtained by the present method contain a higher proportion of renal cortex than those taken with a Vim-Silverman needle, and are therefore more useful to the histologist.

I am indebted to Dr. Charles Warwick and Miss J. Young, and their colleagues, for valued cooperation in the radiological department; to Prof. George Smart for advice and encouragement; and to the physicians who kindly allowed access to patients under their care—Prof. George Smart, Prof. S. D. M. Court, Dr. A. G. Ogilvie, Dr. T. H. Boon, Dr. F. J. W. Miller, Dr. G. A. Neligan, and Dr. G. O. Richardson.

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EXPERIMENTAL STAPHYLOCOCCAL INFECTIONS IN MAN

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THE earliest attempt to test staphylococcal virulence in man was made by Garré (1885), who rubbed an entire slope culture into the skin of his forearm. This resulted in multiple pustules from which a carbuncle later developed. Since this dramatic demonstration of staphylococcal virulence little experimental work has been performed in man, for obvious reasons. Recently, however, Elek (1956) and Elek and Conen (1957) injected staphylococci intradermally and were able to produce small pustules with doses of over a million organisms; they were unable to produce lesions with killed cocci, and the addition of toxin did not influence the outcome.

In the experiments we describe here we attempted to simulate more closely the conditions obtaining in a wound by using artificial skin lesions into which staphylococci were introduced. By this method we hoped to determine whether local conditions influenced multiplication of organisms or the course of the subsequent lesion, whether different types of staphylococci varied in pathogenicity, and what was the smallest infecting dose.

TABLE I—PHAGE-TYPE AND SOURCE OF *Staph. aureus* USED IN EXPERIMENTS

Phage-type	Source
n.t.	Perineal carrier
n.t.	Nasal carrier
47/77	,, ,,
52/80	,, ,,
3c/55/71*	Septic wound

n.t. = not typable with the routine set of phage.
* = this organism was obtained from an outbreak of wound sepsis (Foster 1960).

Materials and Methods

The strains of staphylococci were isolated on blood-agar and identified by their colonial appearance and slide-coagulase tests. The strains were stored on agar slopes in bijou bottles, and then phage-typed by the method of Anderson and Williams (1956). The phage-type and origin of the various organisms used in these experiments are listed in table I. All were coagulase-positive *Staphylococcus aureus* (with the exception of a coagulase-negative *Staph. albus* used in one experiment), and all were sensitive to the standard antibiotics.

The experimental lesions were made by scraping the epithelium from a small area of skin on the volar surface of the forearm (Rebuck and Yates 1954). Using a scalpel with a small blade, twenty-five strokes were made, this manœuvre resulting in a lesion of constant size which did not bleed, but in the base of which capillary loops were easily visible. The lesions produced in this way were inoculated with a standard platinum loop delivering about 0·005 ml. of an overnight ' Lemco ' broth culture containing about 250×10^6 organisms per ml. The standard inoculum was thus approximately 10^6 organisms. The lesions were then sealed with circular flamed coverslips which were held in position with ' Sellotape '.

TABLE II—COMPARISON OF THE MULTIPLICATION OF ORGANISMS IN STANDARD SKIN LESIONS SEALED WITH COVERSLIPS AND LEFT EXPOSED

Time after inoculation	No. of organisms recovered	
	Lesions sealed with coverslips	Lesions allowed to dry
15 min.	$0{\cdot}7 \times 10^6$	$0{\cdot}7 \times 10^6$
2 hours	$1{\cdot}8 \times 10^6$	$0{\cdot}5 \times 10^6$
5 ,,	..	$0{\cdot}4 \times 10^6$
8 ,,	18×10^6	$0{\cdot}8 \times 10^6$
17 ,,	25×10^6	..
27 ,,	55×10^6	$2{\cdot}6 \times 10^6$

Staphylococcal Counts from Skin Lesions

The coverslip and sellotape over each lesion were stripped off and dropped into 10 ml. of nutrient broth in a wide-mouth universal container. One drop of sterile broth was then added to the underlying lesion, and the whole area was thoroughly rubbed with two sterile alginate wool swabs to remove all exudate and superficial layers of the lesion. Both swabs were then broken off into the same sample of nutrient broth as the coverslip. After capping, the universal container was shaken vigorously until the alginate swabs disintegrated.

Serial tenfold dilutions were then prepared in broth using $^1/_{50}$ ml. dropping pipettes, and each dilution was plated out. After overnight incubation the colonies of staphylococci were counted, and from these counts the number recovered from the whole lesion was calculated. In experiments in which coverslips were not used to seal the lesions organism counts were obtained by firm swabbing of the area with alignate swabs after preliminary moistening with broth. The swabs were then dropped into the universal containers as before.

Results

Multiplication of Organisms

Five standard skin lesions were made in two subjects and inoculated as described above with phage-type 3c/55/71. In one subject the lesions were covered with coverslips, and in the other they were left exposed. Counts were then made of the numbers of organisms isolated at various times after inoculation.

It will be seen from table II that the covered lesions showed considerable increase in the numbers of organisms between 2 and 8 hours, followed by a slower increase over the next 14 hours, whereas there was virtually no increase in numbers in the uncovered lesions even after 24 hours. Macroscopically, the covered lesions showed a purulent exudate after a few hours in contrast to the uncovered lesions, which formed a scab with scanty exudate.

Effect of Foreign Material

In view of the possibility that foreign material might influence the results, the effect of rubbing starch and french chalk into the lesions was investigated.

Six standard skin lesions were made and treated as indicated in table III. They were then covered with the lids of small bijou bottles which were strapped on to the arm, keeping the lesions moist but avoiding the direct pressure inevitable with a coverslip. The lesions were left for 24 hours, after which they were inspected and organism-counts were made.

TABLE III—COMPARISON OF ORGANISM-COUNTS AND MACROSCOPIC APPEARANCES IN LESIONS TREATED WITH FOREIGN MATERIAL

Lesion	Appearance at 24 hours	Organism-count at 24 hours	Appearance at 48 hours
1. Control	Serous exudate	0	No erythema
2. Standard loopful of staphs.	Purulent exudate	19×10^6	Erythema+
3. Standard loopful of staphs.+ french chalk	,, ,,	17×10^6	,,
4. French chalk ..	Dry lesion	0	No erythema
5. Staphs.+starch ..	Purulent exudate	13×10^6	Erythema+
6. Starch	Slight serous exudate	0	No erythema

The results show no apparent macroscopic difference between the lesions produced in this series and those in which coverslips had been used, although the rate of multiplication of organisms was slower with the bijou-cap method. There was also no significant difference between the lesions to which foreign material had been added and those which were uncontaminated.

Inflammatory Responses in Skin Lesions Infected by Staphylococci

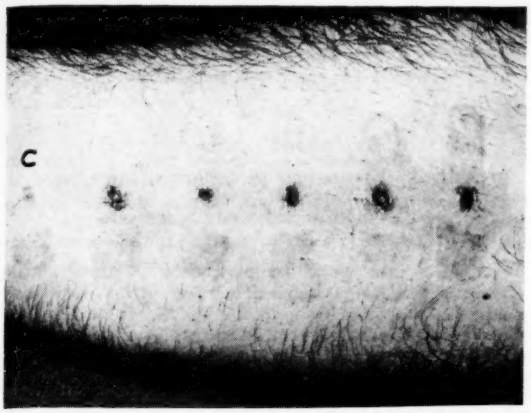
Three skin lesions were made, one of which acted as a control, while the other two were inoculated with a standard loopful of a 24-hour culture of *Staph. albus* or *Staph. aureus* (phage-type 3c/55/71) respectively (table IV). The lesions were then sealed with coverslips, which were changed at intervals during the next 24 hours. The cellular exudate on these coverslips was stained by methylene-blue and examined microscopically. The state of the lesion was recorded after 24 hours.

The essential cytological difference between the infected and the control lesions was the increasing numbers of degenerate polymorphonuclear leucocytes in the infected lesions, whereas

TABLE IV—COMPARISON OF THE INFLAMMATORY RESPONSES IN SKIN LESIONS INFECTED BY *Staph. albus* AND *Staph. aureus*

Time of application of coverslips	Cytology	Control (uninoculated)	*Staph. albus*	*Staph. aureus*
5–8 hours ..	Polymorphs	++	++	++
	Degenerate polymorphs	−	+	+++
	Mononuclears	++	++	+
	Staphylococci	−	+	++
9–13 hours ..	Polymorphs	++	++	++
	Degenerate polymorphs	+	++	+++
	Mononuclears	+++	++	+
	Staphylococci	−	+	++
13–24 hours	Polymorphs	++	++	+
	Degenerate polymorphs	+	+++	++++
	Mononuclears	+	+	+
	Staphylococci	−	++	+++
Macroscopic appearance at 24 hours (see figure)	..	Serous exudate; no erythema	Seropurulent exudate; no erythema	Purulent exudate surrounding erythema+

+ = scanty; ++ = moderate number; +++ = numerous.



Comparison of the control skin lesion, C, and lesions inoculated with five different types of *Staph. aureus*.

in the control lesion mononuclear and histiocytic cells increased for 13 hours, when they dominated the picture. Although phagocytosis of organisms by polymorphs was seen on all the coverslips from the infected lesions most organisms were extracellular.

Different Types of aureus and Their Inflammatory Responses

Six standard skin lesions were made; five of these were inoculated with the five different types of *Staph. aureus* listed in table I. The lesions were then sealed with coverslips which were changed at intervals, as already described. After 24 hours all the inoculated lesions showed surrounding erythema and were covered with a purulent exudate, whereas the uninoculated lesion was not erythematous and showed only slight exudate (see figure). There was no essential difference between the lesions produced by the different types of organisms.

Organism Dose and Inflammatory Response

Two sets of five standard lesions were made and inoculated with dilutions of a 24-hour broth culture of *Staph. aureus* (phage-type 3c/55/71). Four of the lesions of one of these sets were inoculated with 100, 1000, 10,000, and 1,000,000 organisms respectively, while the other set was seeded with 240, 120, 60, 30, and 15 organisms. In each set the fifth lesion was inoculated with broth as a control.

The results of the larger dose inoculum are shown in table V. There was little difference between lesions 2, 3, and 4 although the exudate was increased slightly with increasing numbers of organisms. Lesion 5, however, by contrast showed a frankly purulent exudate, and it was indurated and sore. After removal of the coverslips all these lesions dried up and were healed within a week.

The results of the smaller dose inoculum, shown in table VI, indicate that as few as fifteen organisms are sufficient to cause a septic lesion, and they illustrate the rapidity with which the organisms can multiply.

The Staphylococcal Lesions

In the course of these experiments, two of the three subjects developed skin lesions of some severity on the inoculated arm. Soon after inoculation one got a boil and a crop of small pustules in the hairy part of the arm and over the sites of a sellotape reaction; 5 weeks after his last inoculation he developed a further boil in the same area. The organisms from these lesions all belonged to phage-type 3c/55/71. The other subject, who also had some boils on the arm immediately after inoculation, got a large boil on the thigh as well 2 weeks after the last inoculation of organisms. This subject, who had never previously been a nasal carrier of *Staph. aureus*, was at that time found to be carrying phage-type 3c/55/71 in his nose. The boil on his thigh resolved with local treatment, and the nasal carriage was cleared up with a cream containing chlorhexidine and neomycin (' Naseptin '). But 2 weeks later a large abscess developed on the buttock, from which was again grown phage-type 3c/55/71. Before this abscess appeared he had not been a perineal carrier of *Staph. aureus*.

TABLE V—COMPARISON OF ORGANISM-COUNTS AND MACROSCOPIC APPEARANCES OF LESIONS TREATED WITH DIFFERENT DOSES OF *Staph. aureus*

Lesion	Appearance at 24 hours	Organism-count at 24 hours
1. Control	No exudate; no erythema	0
2. 100 organisms	Seropurulent exudate; erythema 5 × 5 mm.	$5{\cdot}2 \times 10^6$
3. 1000 ,,	Seropurulent exudate; erythema 7 × 7 mm.	$8{\cdot}0 \times 10^6$
4. 10,000 ,,	Seropurulent exudate; erythema 7 × 7 mm.	$11{\cdot}0 \times 10^6$
5. 1,000,000 ,,	Purulent exudate; erythema 15 × 15 mm.	$21{\cdot}0 \times 10^6$

Discussion

Despite the extensive reports which have accumulated on the epidemiology of staphylococcal infections, the factors which determine the development of septic lesions in any person remain largely unsolved. Although clinical evidence suggests that certain phage-types of staphylococci are more virulent than others (Barber and Burston 1955), and that passage through a septic lesion also enhances virulence (Beavan and Burry 1956), there is no direct experimental evidence that different strains of *Staph. aureus* differ in virulence. Elek (1956) and Elek and Conen (1957) attempted to test the behaviour of staphylococci in man by injecting them intradermally. They produced small septic lesions with 1–5 million organisms, but were unable to demonstrate any difference in the smallest pus-forming dose between strains obtained from lesions or from healthy nasal carriers and epidemic strains.

TABLE VI—DETERMINATION OF THE SMALLEST INFECTING DOSE

Organisms applied	Organisms recovered at 24 hours	Macroscopic appearances at 24 hours
240	$18{\cdot}5 \times 10^6$	Seropurulent exudate with erythema
120	$10{\cdot}5 \times 10^6$	
60	$11{\cdot}5 \times 10^6$	
30	$11{\cdot}0 \times 10^6$	
15	$6{\cdot}1 \times 10^6$	
0 (broth only)	0	

Using a similar organism dose we have shown that it is possible to demonstrate differences in skin reaction between an uninfected lesion, one inoculated with *Staph. aureus*, and one inoculated with *Staph. albus*. The *Staph. albus* lesion was clearly infected in contrast to the control but the inflammatory reaction was less than in the lesion infected by *Staph. aureus*.

In a similar experiment four types of *Staph. aureus* which had not been associated with infections were compared with a strain (phage-type 3c/55/71) known to have caused several infections. It was not possible to differentiate between the macroscopic or microscopic features of these five lesions at the end of 24 hours: all showed a similar purulent exudate with surrounding erythema. These results confirm those of Elek and Conen (1957), who also attempted to differentiate between lesions produced by organisms from carriers, and those from septic lesions, without success.

The multiplication of staphylococci in these standard infected lesions covered with coverslips followed the expected pattern of growth, with a lag phase followed by a phase of rapid multiplication. But in similar experiments in which the lesions remained uncovered after inoculation, multiplication was delayed for 8 hours. It seems probable that keeping the lesion moist was the significant factor since the 24-hour count after a standard inoculation was similar whether the lesions were covered with coverslips,

or with small lids which retained moisture without causing pressure on the lesion. No evidence was forthcoming that the application of foreign material, such as french chalk or starch, which are used in glove powders, influenced the multiplication of organisms or the 24 hours' inflammatory response. Superficial foreign material, however, cannot be compared with deep foreign bodies, such as sutures. The experimental work of Elek and Conen (1957) has shown that sutures have a significant effect in determining a clinical lesion.

In all the initial experiments in our study the organism numbers in the inoculum were mostly of an order similar to those used by Elek (1956), and thus they bore little relation to clinical reality. In our dilution experiments, however, we found that as few as fifteen organisms could still produce significant sepsis in a standard skin lesion, and also that multiplication of organisms was so rapid that the total organism count at 24 hours was not much different from those infected with larger inocula. In so far as these experimental skin lesions simulated operation wounds, the results indicate that wound infection could also develop after initial contamination with small numbers of organisms. The significance of this finding is enhanced by the observation of Foster (1960), who demonstrated the deposition of occasional staphylococci on an artificial operation site by a carrier using full aseptic technique.

The unplanned subsequent septic lesions in two experimental subjects curtailed further experiments, but illustrated some additional aspects of the behaviour of *Staph. aureus* in the body. The boils on the arms were not necessarily at the site of inoculation but were always centred on hair follicles. These findings are in line with clinical experience and with the experimental work of Bockhart (1887), who excised experimentally produced furuncles and showed histologically that the organisms had multiplied in hair follicles. It may be of significance in this connection that of the three subjects of this experiment the one who escaped infection entirely was a woman, and the one most severely affected was the most hirsute. This subject, who later became a nasal carrier and developed abscesses on the thigh and buttock, illustrates the propensity of the *Staph. aureus* to spread all over the body from an initial infective site, and the importance of separating such infected individuals from the neighbourhood of uninfected healing wounds.

Summary

Artificial skin lesions produced in man were inoculated with staphylococci. Organisms multiplied rapidly if the lesions were kept covered. There was a difference between the inflammatory response produced by *Staphylococcus albus* and *Staph. aureus*, but no evidence that different types of *Staph. aureus* varied in their virulence.

The addition of superficial foreign material did not affect the eventual lesion. Multiplication of organisms with the production of a septic lesion could be produced by as few as fifteen organisms.

The experiments had to be terminated because of the development of other septic lesions in two of the subjects.

Our thanks are due to Dr. E. H. Letchner who volunteered to take part in one experiment and to Prof. Ronald Hare for helpful criticism.

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"BURNING LIPS" ASSOCIATED WITH ŒSOPHAGEAL REFLUX

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BECAUSE of the unusual presentation, three cases in which œsophageal reflux was shown radiographically are reported.

Case-records

Case 1.—A man, aged 60, employed in a wallpaper factory, complained that for the previous two years he had been constantly troubled by a burning sensation of the tongue, lips, and inside of the mouth generally; this had been worse for the past nine months. He had had colitis, but the last attack was five years ago. He admitted that for many years he had "brought up a lot of wind", especially after meals. He said that he could taste food long after a meal had been taken, and that he had a foul taste in his mouth for most of the day.

The lips appeared normal. The whole of the buccal mucosa was reddened, but the reddening was less intense over the surface of the hard palate under the upper dental plate.

The patient was sure that his dentures had nothing to do with the condition since it had failed to improve when he left them out for several weeks. Patch tests, using denture materials, were negative. Hydrocortisone preparations applied locally to the buccal mucosa, sedatives, and injections of 'Parentrovite' had no effect on the condition. He was not anæmic. Because he worked in a wallpaper factory, his urine was examined for excessive amounts of arsenic, which, however, were not found.

Despite the absence of pain in the chest or the abdomen, the acid taste in his mouth, together with eructations of copious wind, might have been due to a lesion of his œsophagus. A barium swallow showed a sliding hiatus hernia. There was free reflux. Some coarsening of the mucosal folds, compatible with œsophagitis, was seen in the lower œsophagus. No abnormality was demonstrated radiographically in the stomach or duodenum.

He was advised to sleep propped well up on pillows to reduce nocturnal reflux, and to take 'Nulacin' tablets regularly; but, despite several months of medical treatment, the symptoms have persisted. Œsophagoscopic examination is to be made, and, if necessary, the hiatus hernia will be treated surgically.

Case 2.—A man, aged 52, complained of recurrent swellings of the lower lip, together with a burning sensation, and sometimes blistering and superficial ulceration of the lower lip for the past seven months. He said he had a most "foul and disgusting" taste in his mouth, particularly in the mornings. For many years he often had to rise at night and wash out his mouth because of the "dreadful acid taste."

No blistering was seen, but there was some superficial denudation, resembling aphthæ, of the buccal surface of the lower lip. There was no erythema of the buccal mucosa, which was perfectly normal in all other areas. Leaving his dentures out for six weeks had no effect. There was no association with any particular food or drink. Just before the onset of the condition, he had fallen down stairs; and, after this accident, he had a pain in his neck. Because of this pain, he was unable to tolerate his usual number of pillows in bed, and had developed the habit of lying flat.

Barium meal showed that there was no hiatus hernia; but, with the patient in the Trendelenburg position, barium was regurgitated into the lower œsophagus.

In this case the newly acquired habit of sleeping flat seems to have been responsible for the onset of the burning sensation and for the superficial ulceration of the lower lip. He was advised to raise the head of his bed on blocks.

Case 3.—A woman, aged 65, complained of a metallic taste in the mouth for the past six months. She also complained that her tongue was sore, and that she was troubled by soreness of the lips associated with small painful erosions on the buccal

mucosa. She had nocturnal indigestion which was relieved by sitting up in bed.

A barium meal elsewhere showed no abnormality. No amalgam was present in her teeth, and her dentures contained no metal. She was not anæmic.

A barium meal showed some regurgitation of barium into the lower œsophagus when the patient was supine, but a definite hiatus hernia could not be demonstrated.

Discussion

All the patients complained of burning sensations of the buccal mucosa; and, except for case 3, they were free from any abdominal pain or indigestion. They all were shown to produce œsophageal reflux in the supine position.

While aphthosis affecting mucous membranes other than in the mouth must be regarded in a different light, recurrent ulceration of the buccal mucosa, with painful erosions, might profitably be reviewed in the light of this experience. It may be that these lesions, and perhaps those called "dyspeptic ulcers" of the mouth, may in fact be due to the action of gastric secretions on the buccal mucosa.

Summary

Three cases are reported in which the patients complained of burning sensations of the tongue, lips, and buccal mucosa, and of an unpleasant taste in the mouth. Two of them had patches of mucosal erosion, resembling aphthous ulceration.

In all three, when supine, stomach contents were shown radiographically to be regurgitated. One patient had a sliding hiatus hernia, but no such abnormality was found in the others.

Œsophageal reflux is suggested as a possible cause of some so-called " dyspeptic ulcers " of the mouth.

I should like to thank Dr. P. J. Hare and Prof. R. S. Pilcher for permission to publish these cases, and I am most grateful to Dr. K. M. Harvey for drawing my attention to case 3.

THE TREATMENT OF DRUG-ADDICTION

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IN September, 1957, we began to treat three young patients who had become addicted to drugs at an early age and who had never made satisfactory adjustment to life. They professed themselves anxious to be cured; but two had already been deprived of drugs for a short time while serving a prison sentence for obtaining drugs illegally, and both readily admitted that while in prison they thought always of when they would be free and could go back to drugs.

We decided to withdraw the drugs as quickly as possible, to give intensive psychiatric treatment while the patients were in the nursing-home, and to follow this by finding them suitable employment in a new environment. But unfortunately we had underestimated the skill and tenacity of the drug pedlars and their associates.

Each of these patients left the nursing-home without withdrawal symptoms, in a reasonable state of health, and determined to keep clear of drugs. But within a fortnight all three were taking drugs again, and were once more under the control of the pedlars. The method of treatment which had proved successful in alcoholic patients—firstly detoxication and the creation of a sense of wellbeing, and secondly intensive psychotherapy and vitamin therapy—was evidently useless for these drug addicts. It was obvious that before withdrawal there must be a preliminary period during which the patients were adequately prepared, both psychologically and physiologically, for complete withdrawal of the drugs of addiction.

If the patient was to make a successful effort to face life without drugs, especially when crises arise, there must be a strong enough incentive to seek treatment, and sufficient insight to realise that personal difficulties are a major factor in the illness. A negative attitude—e.g., asking for help because of difficulties with the authorities, or domestic or financial problems—was only effective for a comparatively short time. It was also essential that the patient should realise clearly that withdrawal of drugs alone would not free him from a recurrence of craving for the effects of the drug.

The Series

We have excluded from our later series patients from whom we did not obtain a life-history which could be verified, and also those who were addicted to barbiturates and tranquillisers. The remaining fifty-one patients were treated between August, 1958, and March, 1960. The earlier ones were referred to I. M. F. from P. M. S.'s general practice; most of the others were advised to seek treatment by patients already treated. They fell into 3 main groups:

Group 1

Nine patients, aged 28–47, for adequate medical reasons, had been given narcotic drugs—morphine, 'Omnopon', or pethidine—and had continued to obtain a supply of the drug, legally or illegally, after the original need had passed. All probably had a low threshold for pain and discomfort, and they had developed a low threshold for anxiety; detailed analyses revealed underlying personality difficulties. None of these patients used diamorphine (heroin) or cocaine, and only one resorted to forging prescriptions in order to obtain pethidine. Drugs were obtained either wholly or partially from a medical practitioner, extra supplies being acquired illegally.

Group 2

Six patients, aged 45–55, came from the higher social and economic levels, and had relatively high intellectual achievements. They had taken drugs originally " in order to live more fully ", and three of them had lived reasonably useful lives for over 20 years after becoming addicted.

Those receiving medical prescriptions for their entire supply of drugs were able to maintain a reasonable social and economic level, but those buying from pedlars to supplement supplies went steadily downhill and eventually were unable to provide regular food and adequate lodging. The energy and concentration which should have been devoted to making a success of a profession or business were directed to the pursuit of drugs, which alone could give relaxation, a sense of security, and freedom from anxiety. All six patients had taken both heroin and cocaine.

Group 3

The largest group of thirty-six patients had many characteristics in common despite individual differences. Their ages ranged from 18 to 32 years. Behind most were broken homes, unhappy parental relationships, lack of discipline or (less often) too rigid discipline, and either lack of security or over-indulgence by one or both parents, which had resulted in inability to adapt to the normal hazards of life.

These patients were immature, inadequate, and unstable; they had failed to develop normal relationships with family and friends, and lacked willpower or any form of self-discipline. They had a low threshold for pain and discomfort, were unable to tolerate criticism, and equally unable to bear frustration. They lived for the immediate gratification of their desire for drugs, and were totally without concern for the welfare of

others. Any crisis or difficulty was followed by urgent demands for an increased supply of drugs.

They avoided responsibility, lacked normal healthy interests and ambitions, and generally failed to keep a job for any length of time. With the increasing loss of power to control the need for frequent intravenous injections they became more unstable and more anxious, and consequently increasingly dependent on drugs for relief of tension. Some seemed capable of maintaining reasonable ethical and moral standards apart from anything connected with the drug. About things even remotely concerned with their drugs they were untruthful and unreliable, making less and less effort to appear plausible.

Among themselves they had a rigid code. They would not inform about associates from whom they borrowed or bought drugs, or to whom they lent or sold. They were incapable of reasonable ethical judgment about the activities of the pedlars, especially those who were also drug-addicts. On the contrary there was grudging admiration for their ability, and a peculiar snobbishness about the fact that social distinctions vanished in the common pursuit of drugs.

They were completely self-centred and selfish, and showed little emotion except over their own problems. While assured of what they regarded as an adequate supply of drugs—which they considered they had a right to demand—their behaviour and capacity for an average day's work often appeared more or less normal, but if this supply was not forthcoming they were overwhelmed by the need to obtain it immediately and at any cost, resorting to forging prescriptions or other crimes.

The actual drugs taken are important in determining the patients' behaviour. The few who were satisfied to take morphine or omnopon without cocaine were able to lead comparatively useful lives unless they became involved in selling drugs to pedlars or other addicts. Most took both heroin and cocaine, and although cutting down the amount of cocaine produced no withdrawal symptoms any suggestion of reducing the dose was met by resistance and even violent reactions. Fantastic stories were offered in efforts to obtain extra cocaine, but the most common pretexts were " accidents " which happened while they were preparing the cocaine for injection. They also pleaded that if only the cocaine could be increased, then they would find it easier to cut down on the heroin.

In six of this group of thirty-six addicts detailed histories and psychiatric treatment revealed significant differences. Each had a good cultural, social, and economic background, and only one had a history of a broken home and lack of normal parental discipline and security. Two were musicians, one a writer, the fourth had many friends who were musicians, and the other two were Americans who had become drug addicts here and in Paris, and who were anxious to return to America.

Treatment

In the early stages of treatment, before withdrawal was started, the patients were seen in I. M. F.'s consulting-room. For the actual withdrawal they went into private nursing-homes. The treatment was divided into two phases:

Phase I

While the patient was being stabilised on his drugs, freed from dependence on pedlars, and helped to acquire self-respect and self-confidence, treatment was mainly psychotherapeutic.

A major difficulty in the early stages of treatment was the inability of any patient to be absolutely truthful. It was obvious that all of them were supplementing their legitimate supplies from the black market, and at first it was difficult for them to realise that adequate supplies could be obtained legitimately. We made it clear to them that, while the ultimate aim was to free them from need for the drug, we were not prepared to go on writing prescriptions for drugs indefinitely, but they would be given a supply of drugs while they were being stabilised and freed from black-market activities, both financially and morally.

A minor difficulty during this period was their inability to say simply that they had overstepped the usual amount. Instead they either augmented their supplies from the black market, or produced plausible stories of accidents or losses. Eventually they realised that it was better to state bluntly that too much had been used. Extra supplies were prescribed to prevent them returning to the black market, which would involve them in financial difficulties, and (which is even more important) would mean a return to the degradation and humiliation of contacting the pedlars. It was also made very clear that borrowing and lending would not meet with approval, but selling of drugs would be disastrous.

Many of these patients were malnourished, especially those in the third group. In addition they were abnormally dependent on barbiturates, especially pentobarbitone (' Nembutal '). Vitamin therapy was useful in treating the malnutrition, and the problem of the barbiturates was dealt with by substituting ' Mylomide ' (a combination of amylobarbitone and bemegride) and reducing the amount before the withdrawal treatment.

The formation of abscesses after careless injection was an ever-present trouble, and frequently necessitated surgical intervention.

During this phase of treatment the patients acquired enough insight into their condition to be able to cooperate, and they also acquired confidence.

Phase II

During the period immediately before withdrawal treatment, chlorpromazine (' Largactil ') or perphenazine (' Fentazin ') was given to control anxiety and tension, and promethazine (' Phenergan ') to potentiate the sedatives which were necessary to promote restful sleep. When the patient was in reasonably good physical condition, and for 10 days before withdrawal, concentrated vitamin (' Parentrovite ') and amiphenazole (' Daptazole ') injections were given at regular intervals.

The drug was withdrawn as rapidly as possible, depending on the severity of the withdrawal symptoms. The patients were assured that they would not be allowed to suffer severe symptoms, and this promise was strictly kept. This was important, because if they relapsed they would not be afraid to return for further treatment. No two patients reacted in exactly the same way, but all were restless, had some pain in the legs and back, and complained of weakness.

As the dosage of each drug, including the barbiturates, was cut down, an effort was made not only to decrease the amount of heroin, morphine, or cocaine, but also to reduce the frequency of injections and to substitute intramuscular for intravenous injections. These efforts met with varying degrees of success, especially when the ritual of the intravenous injection was threatened.

By frequently substituting one pill of heroin gr. $^1/_{12}$ for one of heroin gr. $^1/_6$, and by very gradual reduction of the amount of cocaine, it was possible to decrease the dose considerably without the patient's knowledge and without any psychological protest. It was essential meanwhile to see the patient daily, and to guard against any symptoms of withdrawal, however slight. Amiphenazole given during this period was undoubtedly helpful. Most addicts objected to adding the amiphenazole to their injection of drugs because it interfered with the subjective effects, but they all appeared perfectly willing to take it as tablets or separately as an injection.

Generally it proved expedient to cut the dose of heroin and morphine rapidly, and to give 4-hourly amiphenazole injections during the day. Cocaine was cut more slowly. Perphenazine injections were given to control the anxiety and restlessness which were especially troublesome in the evening. Vitamin therapy was further increased during the actual withdrawal period and parentrovite was given twice daily. Fruit juice, carbohydrate drinks, and milk were given throughout.

Results

With one or two exceptions all these drug-addicts are still under observation. Each patient differed in response

to the withdrawal of heroin, morphine, and cocaine. Many were more resistant to the reduction of cocaine than to reduction of heroin or morphine. The results in each group are:

Group 1

All nine patients are now independent of drugs.

Group 2

Three patients are completely free from dependence on drugs, two are taking small doses of morphine and are under control, and the sixth is moderately controlled but still takes morphine and cocaine and continues to deteriorate slowly.

Group 3

Among this group were six addicts who proved resistant to treatment. Four were psychotic, one was of very low intelligence and incapable of acquiring any insight into her condition, and the sixth was preoccupied with keeping in close touch with other addicts and supplying them, when need arose, with small amounts of heroin or cocaine at vast cost.

Three other patients are not under satisfactory control; one borrows and lends drugs at intervals, and the other two almost certainly sell and then report that they have had an "accident".

Seven patients' drugs are slowly being cut down, and they intend to stop them entirely.

Twenty patients have been freed from dependence on drugs. Four of them who relapsed when faced with major difficulties or disaster reported back almost immediately and asked to be cleared again.

In a few of the earlier cases mild convulsions and spasm of the neck and jaw muscles proved troublesome during the withdrawal phase, but preliminary reduction of the barbiturates and the other premedication almost completely eliminated this complication. Visual hallucinations also were less frequent after premedication.

Two or three patients experienced a short panic reaction when they realised that the heroin or morphine had been completely stopped. Later they were willing to discuss plans for the future, and to accept that they must cooperate in protecting themselves from the activities of the pedlars, their associates, and also their own friends.

They realised that they must either avoid conditions of stress and danger or, if this were impossible, exercise conscious discretion and aim ultimately at making a fresh start in a new environment.

Convalescence was sometimes difficult to arrange except for private patients, because we were unable to find any convalescent home which would accept drug-addicts. Those who were able and willing to get away from their old associates and surroundings found it easier to adjust to life, and to remain without drugs. They developed a sense of wellbeing, put on weight, and were able either to undertake light work or, in most cases, to return to normal employment within a comparatively short time.

Discussion

Any psychiatric therapy which offers constructive help to the addict must be based on understanding of the whole individual personality, and adjusted to individual needs. It is therefore important to study the development of the personality, the hereditary and constitutional factors, and the reaction to the environment. Such success as we have achieved is largely due to treating each patient as an individual, and not as one of a group. Analysis of the patients' reactions and the dynamic factors involved helped them to understand themselves, their difficulties, and their pattern of behaviour in life situations. The aim of treatment was to enable them to achieve the ability to deal with anxieties, to understand and accept their limitations, and to tolerate emotions which rise from frustration. Insight is not enough. They must try to control and strengthen personality weaknesses, for security must be based on self-reliance combined with the ability to become an integrated member of society.

All the patients who have been cleared of dependence on drugs, or who are under treatment, realised that drug addiction had become the only important thing in life, and that the original reason for taking heroin and cocaine had become less important than the ritual of each intravenous injection. Not one of them was a normal well-balanced personality; all had had symptoms of anxiety and lacked self-confidence, but on the surface they appeared to be leading reasonably normal lives. Those who had to obtain or supplement their supplies from the regular pedlars bitterly resented the degradation of being dependent on them, and also begrudged their excessive charges for a few pills or a few grains of powder.

The incentive to be free from drug addiction was strong and the patients cooperated well, especially after it had become clear that they could be freed from the pedlars and other black-market activities. They later came to appreciate the factors which had been responsible for their condition, and how rapidly they were approaching the point of no return. All realised that it was impossible to contemplate controlled addiction, and even the musicians accepted the possibility of living and working without the help of drugs.

As a result of our interference with the activities of the black market we are now able to treat our patients with more hope of success, especially since one and then another of the best-known figures in the black market have become our patients because the market has died away.

Summary

Fifty-one drug-addicts, treated between August, 1958, and March, 1960, fell into 3 groups:

1. Nine patients who were originally given morphine, heroin, or pethidine for adequate medical reasons had continued to obtain supplies of the drug. All are now clear of dependence on drugs.

2. The oldest group of six patients came from a higher social and cultural level. Three are now clear of dependence on drugs; two are still taking small doses, but they are under control and intend ultimately to stop; and the sixth is under moderate control but seems likely to deteriorate slowly.

3. Of the largest group of thirty-six patients, aged 18–32 years, twenty have been cleared of dependence on drugs, ten are still under treatment, and six have proved resistant to treatment.

"... The ability to provide the kind of setting in which those who are mentally ill or emotionally disturbed can still function to the best of their abilities, without the stigma that traditionally attaches to the word 'mad' is an important challenge to the contemporary industrial society of the Soviet or American type. . . . The main contribution the Soviets have made, lies, probably, in their concepts of not condemning psychotic patients to the idle, demoralizing, de-socializing, untherapeutic and wasteful life of the chronic patient in the large mental hospital. Concomitant with this approach is the bringing of psychiatric care into the community, even into the patient's home if necessary, and the linking of this treatment with the general network of medical facilities maintained under a system of socialized medicine. By contrast, it may be that their contribution to the treatment of the neuroses is hampered both by the collectivistic nature of their social order and philosophy, and the dogmatic intolerance of schools that do not fit their theoretical and ideological commitments."—MARK G. FIELD, PH.D., *Social Problems*, 1960, **7**, 277.

Medical Societies

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE

AT a meeting in London on Dec. 8, Sir William MacArthur, the president, on behalf of the American Society of Tropical Medicine and Hygiene presented the Walter Reed medal to Sir Gordon Covell.

Hookworm Disease and Anæmia

Dr. E. VAN OYE (Belgium), in a paper read in his absence by Dr. L. G. GOODWIN, drew attention to the high incidence of hookworm infection among inhabitants of the Belgian Congo and Ruanda-Urundi and the high degree of morbidity ascribed to the infection. Bephenium (' Alcopar ', Burroughs Wellcome) had been found to be effective, non-toxic, and easy to administer without previous preparation. The drug was, therefore, very suitable for mass treatment.

Dr. G. J. STOTT had carried out an investigation in Mauritius, on behalf of the World Health Organisation, following a preliminary survey there by Prof. A. W. Woodruff. Dr. Stott had found that hookworm infection with hypochromic microcytic anæmia was very common. Such infection had been present in 88% of 284 anæmic patients, and the anæmia responded well to iron therapy, significant improvement being obtained with as little as 6 mg. of iron per day even without prior anthelminthic treatment. The national diet provided only 10·2 mg. of iron per head per day, and among certain groups the amount was as low as 6 mg. The diet was in fact so low in iron that even moderate hookworm loads could cause sufficient blood-loss to precipitate anæmia. Enrichment of the national diet with iron was likely to prove the most effective single public-health measure against anæmia in Mauritius.

Dr. HENRY FOY and Dr. ATHENA KONDI reported that the use of radioactive iron and chromium had established that intestinal blood-loss from infections with 1000–3000 hookworms ranged from 50 to 200 ml. per day. Lack of correlation between the worm load and the presence of anæmia could usually be explained by recent administration either of iron or of vermifuges. Intestinal blood-loss could be reduced to nil by removing the worms, but unless iron therapy was also given no improvement in the hæmatological picture would result because worming did not replace depleted iron stores. Parenterally administered iron had never been required in their series, and gastrointestinal upsets from oral iron had been rare. Blood-transfusion had seldom been required. In some the hæmoglobin could not be raised above 12 g. per 100 ml., and in such cases some other intercurrent infection was usually present. Dr. Foy emphasised the value of periodic vermifuges, in addition to iron treatment.

Prof. A. W. WOODRUFF, opening the discussion, made three points. The first concerned the importance of work on anæmias in the tropics. This importance derived from their extraordinary prevalence, from the clearer idea of their causation on a public-health scale now that malaria was eradicated from so many regions, and from the coming of the World Health Organisation which had provided a stimulus to acquire knowledge on which could be based schemes for elimination of anæmia. His second point concerned the necessity to take into account the time which might be required for hookworm infection to deplete body stores of iron. Until these were depleted, patients might have heavy hookworm infections without anæmia. This had to be noted when considering correlations between hookworm infection and anæmia. Thirdly, it was important to remember that in the tropics anæmias often had a complex ætiology. Patients were commonly infected with several parasites and might also suffer from liver damage and malnutrition.

Dr. O. D. STANDEN drew attention to the resurgence of interest in hookworm infections, partly owing to the introduction of bephenium as a vermifuge.

Sir SELWYN SELWYN-CLARKE doubted the value of dietary fortification with iron so long as patients were being reinfected with hookworms. He emphasised the importance of raising the general standard of hygiene.

Sir GEORGE MCROBERT, however, argued that, though latrines could be provided, it was in many places a time-consuming task to educate the population to use them; and, so far as anæmia was concerned, more good could be brought about by administration of iron costing a few pence than by costly sanitary schemes.

Prof. GEORGE MACDONALD supported the view that supplementation of the dietary iron was an essential means of eradicating iron-deficiency anæmia, and he emphasised that critical analysis still left doubts concerning the causal relationship between hookworm infection and anæmia. The connection might well be there, but it had not yet been proved, and other causes of iron deficiency and of anæmia had to be carefully considered.

HEBERDEN SOCIETY

THE society met in London on Dec. 2 and 3.

In a Heberden oration Dr. JOSEPH J. BUNIM (Bethesda) described 40 cases of Sjögren's syndrome. All but 1 were in women, with a mean age of 50 years. The diagnosis was based on dryness of the eyes, nose, mouth, or throat and on keratoconjunctivitis sicca, xerostomia, and rheumatoid arthritis, at least two of these three conditions being present in all cases. 21 of the 40 patients gave a history of previous drug sensitivity. The serum-albumin was reduced, and the serum-globulin was raised above 3·5 mg. per 100 ml.; this increase was particularly of the γ_2 fraction, which on analytical ultracentrifugation proved to be the 7S type, and the amount of this fraction was raised in most patients with the keratoconjunctivitis sicca complex alone. The test for the rheumatoid factor using bentamite flocculation on whole serum was positive in all cases, and using the sensitised-sheep-cell agglutination test on the euglobulin fraction it was positive in 83% of cases. Anti-nuclear factor was found in 77% of sera; it was present in all cases with myopathy, all cases with keratoconjunctivitis sicca and xerostomia alone, and 60% of cases of rheumatoid arthritis and keratoconjunctivitis sicca, but in only 13% of a control group of rheumatoid arthritis without keratoconjunctivitis sicca. L.E. cells were found in only 3, and these were all cases of rheumatoid arthritis. A high prevalence of complement-fixing antibodies with liver homogenate was found, particularly in the cases of pure keratoconjunctivitis sicca. As the histological changes in Hashimoto's disease closely resemble those in Sjögren's syndrome, examination for thyroid disease was carried out. By the tanned-red-cell technique, thyroglobulin antibodies were detected in 11 of the cases. In only 5 was there evidence of thyroid disease, and in 2 of these section of the gland showed changes consistent with Hashimoto's thyroiditis. Of eleven patients' families studied, eight had 2 or more members with thyroglobulin antibodies, whereas of six control families only one exhibited this feature.

Dr. Bunim concluded that, like systemic lupus erythematosus and rheumatoid arthritis, Sjögren's syndrome was a multi-system disease, and the high prevalence of circulating antibodies to various tissue components in Sjögren's without rheumatoid arthritis was reminiscent of systemic lupus erythematosus. The pathogenic implications of these antibodies was obscure.

Sacroiliac Joints in Juveniles

Dr. MARY CARTER (Canadian Red Cross Memorial Hospital, Taplow) said that dissection of four normal sacroiliac joints

from children had shown broad, smooth, sacral cartilage and thinner, irregular iliac cartilage with radial "splits" bounding a narrow joint space which was deeper in the anterior part of the joint, the most posterior part being largely filled with fibrous tissue. In the case of a child with rheumatoid arthritis who had died at the age of 9 years, and in whom X-ray examination had shown a doubtfully abnormal sacroiliac joint, cartilaginous fusion of this right joint was found without any sign of inflammatory tissue. This might have resulted from the mechanical factor of severe hip disease or previous prolonged immobilisation. In the case of a 20-year-old patient with rheumatoid arthritis, whose pelvic X-ray was normal, post-mortem examination showed changes in both sacroiliac joints with destruction of iliac cartilage and invasion of bony spaces with granulation tissue containing plasma cells and lymphocytes.

Still's Disease

Dr. BARBARA ANSELL and Prof. E. G. L. BYWATERS (Taplow) had in January, 1959, begun to review 264 cases which had been referred as Still's disease. Hitherto 43 had been classed as probable Still's disease. In the follow-up period a definite diagnosis has been made in 20: psoriasis (2), ulcerative colitis (2), further features of classical Still's disease (5), ankylosing spondylitis (2), rheumatic fever (2), osteochondritis (2), systemic lupus erythematosus (1), dermatomyositis (1), Raynaud's syndrome (1), infectious arthritis (1), scleroderma (1). The remaining 23 cases fell into three main groups: (*a*) those with systemic manifestations resembling Still's disease in which rheumatoid arthritis was slight and joint residua were absent; (*b*) those with transient polyarthritis with slight residua; and (*c*) those with less than four joints involved in which residua were common and which might represent a mild form of the disease.

Intervertebral-disc Degeneration

Dr. J. S. LAWRENCE (Manchester) and Dr. JOAN BREMNER (Leeds) had found in population samples in Leigh and Wensleydale that cervical-disc degeneration was uncommon below the age of 25, but the prevalence rose steadily with age, and such degeneration was more common and severe in males of all age-groups. The maximum frequency was at C5. The dorsal region was the most usual site of degeneration; and here it tended to occur earlier and more severely in females than in males, with D7 most commonly involved in females and D8 in males. The lumbar spine was not X-rayed below the age of 35, and by then disc degeneration was found in 35% of males, with L3 most commonly involved; as in the cervical region, involvement was more common and more severe in males. There was a significant relationship between cervical-disc degeneration and neck, shoulder, and brachial pain, the association being greater in females and under the age of 45. In males lumbar-disc degeneration correlated well with incapacity and with back, hip, and sciatic pain. Differences were noticed between urban and rural populations in that the disease was more evenly distributed between the sexes in the rural area, and in this area the changes in the lumbar region were earlier in onset.

Ten-year Follow-up of Rheumatoid Arthritis

Professor BYWATERS, Dr. M. CURWEN, Dr. E. DRESNER, and Dr. A. ST.J. DIXON (Hammersmith Hospital) had followed up 250 cases of rheumatoid arthritis first seen between 1939 and 1948, 125 of them within one year after the onset. As in other series females predominated, and the mean age of onset was about 45. At the ten-year follow-up, 78 of the 250 patients were dead; 76 were in the top two functional grades, and 96 were in the lower three functional grades. Further follow-up information revealed that 131 were now dead. It appeared that in patients who were going to die death was preceded by reduction of functional capacity which was not necessarily from a cause associated with the rheumatoid arthritis—e.g., it might arise from coronary thrombosis. The overall mortality was greater than the expected. Younger patients did better than older, as did males and also those with asymmetrical involvement and fewer joints involved. A negative differential agglutination test (D.A.T.) at follow-up was a good prognostic feature, and females with a negative D.A.T. did better than females with a positive D.A.T. The diagnosis of psoriasis also seemed to be associated with a better prognosis. Death when it occurred was very rarely due to specific complications of the disease, but tended to occur from usual causes before the expected age.

Reviews of Books

Clinical Gastroenterology

F. AVERY JONES, M.D., F.R.C.P., physician, J. W. P. GUMMER, M.S., F.R.C.S., surgeon, Central Middlesex Hospital. Oxford: Blackwell Scientific Publications. 1960. Pp. 652. 70*s*.

THE appearance of a new book by authors distinguished in their subject is always important and exciting. Will they present their experience in a way intended to provoke argument, controversy, and thought: or more factually? Those who expect here a treatise in the first category have mistaken the implication of the title—the emphasis is "clinical"—for this is a work written within the tradition of the British textbook. Each subject is introduced with a list of possibilities either in the pathological or diagnostic sense and followed by amplification in the matter of symptoms, signs, and management in sections devoted to the alternatives. There are exceptions to this general plan; it is inapplicable to the chapters on motility and on torsion and volvulus; it is avoided when trauma is considered. Half the space of the first dozen pages is absorbed by lists. Those who complain that this is tiresome reading should reflect that it is hard to make works of reference readable—and this is a work of reference despite its deceptive size, in which there is frequent allusion to a highly selected bibliography. Furthermore, it is not in any other way hard to digest, for the text is written with admirable clarity, though the type does seem a bit small.

What is lost in personality is gained in orthodoxy; the reader knows that he is treading the right path, that armed with this knowledge he will not go far wrong. The book is therefore appropriate for the postgraduate student rather than the expert. A work, avowedly, of instruction rather than inspiration, it is welcome because it fills an important gap, and valuable because of the industry of its authors in covering the whole of gastroenterology (with the exception of proctology) as seen in the average clinic.

The Femoral Neck: Function, Fracture Mechanism, and Internal Fixation

VICTOR H. FRANKEL, M.D., associate professor of orthopædic surgery, University of Uppsala. Stockholm: Almqvist & Wiksell. 1960. Pp. 120. Sw. kr. 32.

WHEN Smith-Petersen, in 1931, described the treatment of hip fractures by the insertion of a three-flanged nail, it seemed that a solution had been found for what had often been called "the unsolved fracture". Unfortunately recent figures show that, even in the best hands, some 20% of femoral-neck fractures so treated do not unite; and that aseptic necrosis supervenes in about the same proportion of those which do.

This monograph cites some of these figures and recounts briefly the history of the nailing operation before Smith-Petersen (von Langenbeck first nailed a hip in 1878, and Lister did so soon after). Then follows a list of some fifty devices produced during the past thirty years, each of which has been claimed as an improvement on the appliance used by the Boston team. The author's own work has involved a study of the mechanisms of femoral-neck fractures, and of the circumstances under which devices for internal fixation fail, by the use of 'Stresscoat' and strain-gauge techniques. None of the appliances examined were found ideal in form or substance, and, as the author points out, even if one were contrived it could not be placed in the best line for securing the fracture, since this line changes with movements and muscle contractions.

Much of this attractively produced book presupposes a con-

siderable knowledge of mechanics, but it indicates, even to the least mechanically minded, some of the problems which still beset the management of these injuries.

A Synopsis of Public Health and Social Medicine

A. J. ESSEX-CATER, M.R.C.S., D.C.H., D.P.H., D.I.H., F.R.A.I., administrative medical officer of health, City of Birmingham. Bristol: John Wright. 1960. Pp. 576. 55*s*.

IN a foreword to this volume in the well-known series of synopses, designed to meet the requirements of undergraduate and postgraduate medical students, nurses, and others, Prof. J. M. Mackintosh recalls that in the past twenty years developments in social medicine, health education of the public, and mental health have broadened the scope of preventive medicine to an unprecedented degree. Much of the text is devoted to a description of the epidemiology of infectious and non-infectious diseases. Other sections deal with the history of public health, the organisation of the National Health Service, medical statistics, occupational health, environmental hygiene, the care of mothers and young children, the school health service, and mental health. The book ends with a chapter including notes on heredity, the atomic age, and the disposal of the dead. There are some minor errors, and it has not been possible to include some of the most recent legislation, reports, and statistics, but with these reservations the volume can be recommended as a useful summary of public health and social medicine.

The Exercise Book of Dr. Christobel Mendez

Translated by FRANCISCO GUERRA. Editor: FREDERICK G. KILGOUR. Baltimore: Waverley Press. 1960. Pp. 122. $10.

"Galen says that medicine is the science of the healthy, the sick, and the chronic who are neither." So begins the first printed book on the merits of exercise ever written by a physician; and we may judge from the remainder of the work that its author, like many of his later counterparts, found that it was the last-named amongst his patients who taxed him most.

Published in 1553, the book belongs to the great era of scientific writing which had been heralded by the appearance of Vesalius's *De Fabrica* ten years before, and coincided with the description of the pulmonary transit by Servetus in *Christianismi Restitutio*. It is not, of course, to be compared with either of these volumes. Mendez has no original discoveries to announce. He subscribes unreservedly to the old Galenic doctrines and provides further evidence of his credulity by recounting several highly improbable anecdotes. With all his faults, though, he still makes engaging reading. In part because of his sensible and lucid advice upon a hygienic way of life: in part because of his apposite observations upon several matters quite unconnected with medicine. ("Brother," he says, with reference to duelling, "have good temper, and always look at the tip of the sword of your enemy, and you do not need anything else.")

In its present form the treatise has been translated, with a complete reduction facsimile of the old Spanish text appended. We hope its appearance will be the means of acquainting a wider audience with a book of which, in the original, there are only three known copies.

Diagnosis and Treatment of Tumours of the Chest

Editor: DAVID M. SPAIN. New York and London: Grune & Stratton. 1960. Pp. 371. 104*s*.

IF this were the only book on the subject it would be easy to review it wholly favourably, for it covers a large area adequately and provides an easily readable account which is undoubtedly useful to clinicians studying chest tumours. Unfortunately, as with most composite works, it is of uneven merit, with excellent chapters next to ones less good. The variation extends beyond mere style and exhaustiveness. The manner in which the references are dealt with varies from chapter to chapter. Some authors have used the numerical system, making reference to source material easy, others have given the author's name and date in the text, or the name only. In some chapters the references are arranged alphabetically, in others numerically; and in some there are names mentioned in the text but not in the references. This variation is a drawback in a book of this kind, for many chapters are of little value as sources of reference to the more knowledgeable readers, and others may seem too well documented and exhaustive for the postgraduate student. There seems to be a lack of clearly defined purpose in the book's construction; which is a pity, for it contains much of value and much good medical writing.

Manual of Hand Injuries (2nd ed. Chicago: Year Book Publishers. London: Interscience. 1960. Pp. 400. 83*s*.).—The writings of Kanavel and Bunnell gave America a lead in the literature of hand surgery which only a few British authors have yet challenged. This book of Dr. H. Minor Nichols is not the least of the volumes which are maintaining this advantage. It is short, compact, exceedingly comprehensive, and intensely practical. Indeed its scope is so wide, and its instructions so detailed that the introductory caution—that the surgeon dealing with a hand injury must not be tempted into essaying orthopædic or plastic feats for which he has not been specially trained—seems very necessary. Fractures and dislocations, often relegated to a brief final or penultimate chapter, are discussed at length. It is evident that the finger-traction devices of earlier days are now being discarded in favour of intramedullary Kirschner wires, and more rapidly in the United States than in this country. In general, methods advocated throughout are those in favour here, and great emphasis is placed on conservative manœuvres to be adopted in the face of apparently irreparable damage. (The author admits the limitations of vein grafts in an ischæmic arm, and urges deliberate bone-shortening to permit end-to-side arteriorrhaphy.) It seems strange, though, that whenever local anæsthesia is mentioned, the agent suggested is procaine, which most British surgeons abandoned for lignocaine several years ago. This book can be commended in the highest terms as an excellent resumé of the advances which have been made by the opposite side in a subject where there is strong and very friendly rivalry.

Obstetrics (12th ed. Philadelphia and London: W. B. Saunders. 1960. Pp. 1098. £5 19*s*.).—In revising this well-known book, based on the original text of Joseph B. De Lee, Dr. J. P. Greenhill has had much help from 23 contributors. Several new sections and chapters have been added. Increased attention is paid to obstetric factors which may result in fœtal deformity or cerebral palsy; and two of the new chapters are devoted to these important subjects. Like its predecessors, this edition is beautifully produced, and there are many new photographs and diagrams. The work gives a balanced account of modern obstetric practice, and its continued popularity is assured.

Marriage and Periodic Abstinence (2nd ed. London: Longmans, Green. 1960. Pp. 86. 10*s*. 6*d*.).—The theory of periodic abstinence is based on the assumption that ovulation takes place once during each menstrual cycle and that if this time can be identified by temperature readings, and intercourse avoided, then pregnancy will not ensue. For many people this is the only permissible means of avoiding a succession of pregnancies and it is important that the knowledge should be widely available. The intelligent lay person should be able to follow Dr. J. G. H. Holt's explanation and instructions, here adapted by Dr. John Marshall; but these could, with advantage, be presented more simply and clearly. Readers with no religious bias and with complete freedom of choice are likely to disagree with the contention that periodic abstinence is the most satisfactory and effective means of birth control available today.

Textbook of Surgical Pathology (8th ed. London: J. & A. Churchill. 1960. Pp. 704. 75*s*.).—A virtue of this popular work by Prof. C. F. W. Illingworth and Mr. B. M. Dick lay in its brevity, for it enabled the student to encompass the subject within reasonable time. This it still does; but in this eighth edition the bibliography, which is surely important in any concise work of this kind, has been discarded.

THE LANCET

LONDON 24 DECEMBER 1960

More on Leukæmia and Radiation

EVER since the reports of increasing incidence of leukæmia in Japan after the atom-bomb explosions, much attention has been paid to the possible connection between exposure to radiation and the later development of leukæmia. In this country research was stimulated by the suggestion of ALICE STEWART and her co-workers [1] that acute leukæmia in childhood was more likely if the mother had been subjected to much X-ray exposure, say for pelvimentry, during pregnancy and by the demonstration by COURT-BROWN and ABBATT [2] that the incidence of leukæmia was definitely increased among patients treated with deep X-rays for ankylosing spondylitis. Accumulating evidence has, on the whole, failed to substantiate the danger of maternal X-radiation to the fœtus, at least in so far as the incidence of leukæmia is concerned. The latest of these investigations, carried out by COURT-BROWN, DOLL, and BRADFORD HILL,[3] was extensive. Information was gathered about 39,166 mothers who were known to have had abdominal or pelvic diagnostic X-rays in eight hospitals in London and Edinburgh between 1945 and 1956. In 9 of the children of these mothers leukæmia had developed by the end of 1958, whereas the estimated expected number was 10·5. It has been suggested that exposure during the first half of pregnancy may be more dangerous than in the second half; 750 women studied by COURT-BROWN had been irradiated during the first three months of pregnancy but in none of their children had leukæmia developed during an average follow-up of six years. COURT-BROWN et al. review the published data from five other surveys and point out that the evidence is conflicting; in three of these surveys the proportion of mothers who had been irradiated during pregnancy was greater among the mothers of leukæmic children than among mothers of control children; in one there was no difference; and in the fifth the mothers of leukæmic children had been less often irradiated than the controls. COURT-BROWN and his colleagues conclude from their own data that " there is no evidence of any disproportionate occurrence of leukæmia among the children who had been most heavily irradiated nor among the children who had been irradiated early in intrauterine life ". Taking their data together with the published results they do not believe that an increase in leukæmia among children of mothers who have had abdominal irradiation during the pregnancy has been established. A very similar conclusion has been reached by LEWIS [4] who utilised the records of Queen Charlotte's Hospital in London.

Another possible way in which radiation may induce leukæmia is by exposure to radioactive isotopes for the treatment of disease. Radioactive gold and yttrium have been used in the treatment of tumours, but the two diseases in which large numbers of patients have been treated are thyrotoxicosis treated with radioiodine (^{131}I) and polycythæmia vera treated with radiophosphorus (^{32}P). POCHIN [5] has reviewed the 18 known cases of leukæmia that has developed in patients previously treated with radioiodine for thyrotoxicosis; the type of leukæmia was known in 17 cases, and was acute in 13. 10 of these cases occurred in the U.S.A., 4 in Canada, 3 in this country, and 1 in Austria. POCHIN estimates that about 60,000 patients have been so treated in these four countries. In such a population an estimate based on the reported incidence of leukæmia suggests that about 21 (14–28) cases would occur whether or not radioiodine was given. There are, of course, considerable uncertainties in such estimates; patients relieved of their symptoms may cease to attend the clinic, and if leukæmia develops later they may be missed. A routine blood-count before starting treatment may reveal early cases of leukæmia that would otherwise appear as cases developing after treatment; POCHIN notes that in his experience 3 cases were detected in this way. But, making allowances for such uncertainties, POCHIN justifiably suggests that there is no evidence from present records that radioiodine treatment is inducing leukæmia. The effect of radiophosphorus treatment on the incidence of a leukæmic transformation in polycythæmia vera is less easily assessed because the disease can naturally terminate in leukæmia; but in many cases the terminal stage is really a leukæmoid reaction, and SCHWARTZ and EHRLICH [6] found only 1 acceptable case of leukæmia in a critical study of 83 cases. WASSERMAN [7] in 1954 reported 7 cases of leukæmia among 64 cases of polycythæmia, and LAWRENCE [8] in 1955 reported 16 among 231. SZUR et al.[9] have described 2 such cases among a group of 90 treated with radiophosphorus, but both patients had received X-ray therapy earlier in their illness. Other methods—chemotherapy and venesection—are also used for the treatment of polycythæmia. WALD et al.[10], for example, report good results with 'Myleran' (busulphan), and in time we should have a series of patients who have not received radiation treatment and can therefore be used as controls. At present no firm conclusion can be reached about the relative incidence of leukæmia in polycythæmic patients who have or have not been irradiated.

1. Stewart, A., Webb, J., Giles, D., Hewitt, D. *Lancet*, 1956, ii, 447. See *ibid.* 1958, ii, 999.
2. Court-Brown, W. M., Abbatt, J. D. *ibid.* 1955, i, 1283.
3. Court-Brown, W. M., Doll, R., Hill, A. B. *Brit. med. J.* Nov. 30, 1960, p. 1539.
4. Lewis, T. L. T. *ibid.* p. 1551.
5. Pochin, E. E. *ibid.* p. 1545.
6. Schwartz, S. O., Ehrlich, L. *Acta hæmat., Basle*, 1950, **4**, 129.
7. Wasserman, L. R. *Bull. N. Y. Acad. Med.* 1954, **30**, 343.
8. Lawrence, J. H. Polycythemia. Modern Medical Monographs, New York, 1955.
9. Szur, L., Lewis, S. M., Goolden, A. W. G. *Quart. J. Med.* 1959, **28**, 397.
10. Wald, N., Hoshino, T., Sears, M. E. *Blood*, 1958, **13**, 757.

A third source of exposure to irradiation is radioactive tracers, which are being used increasingly in research and diagnosis.[11] In hæmatology radioactive chromium (^{51}Cr, half-life 27 days) is used for determinations of blood-volume, red-cell survival, and blood-loss in the gastrointestinal tract. Diisopropylfluorophosphonate labelled with ^{32}P has been used for estimating the survival-time of platelets. For studies of iron metabolism radioactive iron is extensively used—usually the isotope ^{59}Fe with a half-life of 46 days. Studies of the absorption of vitamin B_{12} have been greatly aided by the use of a vitamin labelled with radiocobalt; at first the isotope ^{60}Co (half-life 5·3 years) was used; today the isotope ^{58}Co (half-life 71 days) is preferred. ANDERSON et al.[12] have lately studied folic-acid excretion by using folic acid labelled with tritium (^{3}H, half-life 12·3 years). The doses of radioactivity applied for any one estimation are carefully adjusted to be well within safety limits. But over a period of time a patient may receive a sizeable dose, perhaps for investigation of disorders in more than one system; and the life of some of the isotopic tracers is far from short. For these reasons it is essential, as HAYTER [11] emphasises, that proper records should be kept now, so that undue exposure can be avoided. The second report of the Adrian committee, which appeared [13] recently, was concerned only with genetic doses, and the estimated annual genetic dose per person from all present uses of radioisotopes in medicine was only 0·18 mr. The committee will doubtless have something to say later about the somatic effect of isotopes.

Perhaps we are over-sensitive about the dangers of radioactive materials. The answer to questions about the use of radiation techniques and treatment is surely, as the Adrian committee emphasises, that they should be used reasonably when clear benefit can be expected, and that they should not be used for routine investigation or treatment when alternatives not involving irradiation are to hand. It would certainly be foolish to abandon radiology in pregnancy, because this may not infrequently be the only means of ensuring safety for mother and child. In some cases of thyrotoxicosis treatment with radioactive iodine may be more suitable than surgery or administration of anti-thyroid drugs, and it apparently carries no greater risk. For polycythæmia chemotherapy can be tried before embarking on treatment with ^{32}P. With regard to radioactive tracers, HAYTER proposes that they should not be used unless there is a clear case for them, and for ordinary diagnostic work

" it is quite often reasonable to dispense with an isotope ' test ' when an equally informative conventional test is available. For instance, when documentary evidence is needed ' for the record ' in a clear case of thyrotoxicosis, it seems proper to estimate the B.M.R. rather than ^{131}I uptake, since the more sensitive differentiation possible with the latter is not needed."

This good advice reminds us that methods involving radioactive materials for investigation or treatment should not be used only because they are easier than conventional methods.

11. Hayter, C. J. *J. clin. Path.* 1960, **13**, 369.
12. Anderson, B., Belcher, E. H., Chanarin, I., Mollin, D. L. *Brit. J. Hæmatol.* 1960, **6**, 439.
13. See *Lancet*, Dec. 10, 1960, p. 1285.

Hartnup Disease

IN 1956 DENT and his colleagues,[1] in a paper entitled " Hereditary pellagra-like skin rash with temporary cerebellar ataxia, constant renal aminoaciduria, and other bizarre biochemical features ", defined a new syndrome which has since become known as Hartnup disease, after the affected family. The full clinical picture appeared in two of four affected siblings who were subject periodically to a photosensitive rash, apparently identical with that of true pellagra, on exposed areas of the body; its appearance was sometimes associated with severe but fully reversible cerebellar ataxia. All four patients had a pronounced aminoaciduria of characteristic and unique paper-chromatographic pattern, and an abnormally large output of certain indolic compounds. Since the disease was first described, nine further cases have been recognised,[2–7] so that the natural history is now better known. This recessive hereditary metabolic disorder manifests itself in childhood, and, unlike most other hereditary metabolic conditions, tends to improve with increasing age: all four affected members of the original family have been completely asymptomatic since 1956.[8] The disorder is probably less rare than might be expected from the smallness of the number of cases so far described; for some of those affected may be symptom-free, and their biochemical abnormality would be unlikely to be uncovered unless they had more severely affected siblings. Although the rash may respond to nicotinamide therapy, dietary sources of this vitamin are apparently adequate. DENT and his colleagues [1] thought it much more likely that an endogenous block in the conversion of tryptophan to nicotinic acid was present. They had difficulty, however, in finding a unifying hypothesis by which to correlate all the clinical and biochemical features.

MILNE et al.,[8 9] having made some careful observations on two affected members of the original family, have provided an elegant and convincing hypothesis which goes far towards explaining the abnormalities in metabolism of indolic and possibly of other aminoacids too. The generalised aminoaciduria of renal tubular origin, without evidence of other defects of renal tubular function, suggested to them a specific defect in the transfer of aminoacids from the glomerular filtrate across the proximal renal tubular cells into the tubular capillary blood. Such a transport defect might not be confined to the renal tubular cells. They therefore designed an investigation to explore the possibility of a similar defect, of tryptophan transport in particular, in the gut, and they demonstrated delayed and incomplete jejunal absorption of L-tryptophan. The high output of indole metabolites for many hours after tryptophan ingestion could thus be explained by the

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2. Hersov, L. A. *J. ment. Sci.* 1955, **101**, 878.
3. Hickish, G. W. *Arch. Dis. Childh.* 1955, **30**, 195.
4. Jonxis, J. H. P. *Ned. Tijdschr. Geneesk.* 1957, **101**, 569.
5. Henderson, W. *Arch. Dis. Childh.* 1958, **33**, 114.
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8. Milne, M. D., Crawford, M. A., Girão, C. B., Loughridge, L. W. *Quart. J. Med.* 1960, **24**, 407.
9. Milne, M. D., Crawford, M. A., Girão, C. B., Loughridge, L. *Biochem.* 1959, **72**, 30P.

action of intestinal bacteria on an abnormally large fraction of tryptophan reaching the colon. In the patients with Hartnup disease, but not in controls, tryptophan was found in the fæces after an oral load. The findings after ingestion of DL-tryptophan (D-tryptophan was not available) suggested delayed absorption of D-tryptophan also. This is further evidence that the absorption of D-aminoacids from the gut is not an entirely passive process.[10] These observations are complemented by the important studies of SHAW et al.,[11] who found that in Hartnup disease ingestion of L-tryptophan produced no increased urinary output of indole metabolites when the gut had previously been sterilised with neomycin.

If the exacerbations of cerebellar ataxia stem from intoxication by indole metabolites, gut sterilisation is a rational method of treating such attacks. MILNE et al.,[8] thinking in terms of intoxication by retained indolic acids, suggest that alkalinisation of the urine would provide an easy and innocuous method of treatment; for they have previously shown [12] that excretion of indoleacetic acid is facilitated in alkaline urine. A possibility which seems equally likely is that the neurological symptoms arise from tryptamine intoxication.[13] Large amounts of tryptophan stagnant in the gut probably give rise to increased production of this amine from the action of intestinal bacterial decarboxylases.[14] When further patients are investigated, a search for abnormal urinary amines should prove fruitful.

DENT and his colleagues [1] originally suggested that an enzyme in the tryptophan/nicotinic-acid pathway might be deficient, and other workers [15] have cast tryptophan pyrrolase in this role. This enzyme is responsible for splitting the 5-membered section of the twin-ringed indole nucleus of tryptophan—the first step in the nicotinic-acid pathway of tryptophan metabolism. Although MILNE et al.[8] sought to test this hypothesis by estimating metabolites of this pathway after oral tryptophan, the information they obtained is probably equivocal because of the jejunal transport defect which was present. An intravenous tryptophan load will probably be necessary in future work designed to elucidate this problem, although the possibility of a transport defect in other body-cells must be kept in mind in interpreting the results.

Despite one or two inconsistencies (such as the inability of MILNE et al.[8] to find evidence of impaired absorption of tyrosine, another aminoacid represented in the aminoaciduria) which probably arise from the inherent difficulties of biological experimentation, the transport-defect hypothesis seems to fit the observed evidence best and accords well with the " one gene, one enzyme " concept of modern biochemical genetics. If the aminoacids excreted in great excess in Hartnup disease all have a similar transport mechanism, then a different transport mechanism or mechanisms probably exist for the unaffected aminoacids. We venture to predict that clinical conditions analogous to Hartnup disease, involving a transport defect of some or all of the basic aminoacids, sulphur-containing aminoacids, prolines, and glycine will be found if watch is kept for them.

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11. Shaw, K. N. F., Redlich, D., Wright, S. W., Jepson, J. B. *Fed. Proc.* 1960, **19**, 194.
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Annotations

QUADRUPLE VACCINE

WE have already argued that the problem of preventing poliomyelitis, diphtheria, whooping-cough, and tetanus might be solved by administering a combined prophylactic early in life.[1 2] In this way the cost of administration would be reduced and the proportion of children immunised would be increased because parents, doctors, and children dislike the large numbers of injections involved in giving each prophylactic separately. The present rate of immunisation is too low to give much confidence that the incidence of these diseases will remain as low as it now is.

One way to ensure that children are immunised is to start the series of inoculations in the first week of life when the mother is in hospital or under medical care at home. Unfortunately, young infants respond less well to antigens than older children. Furthermore antibodies transmitted from the mother interfere with the acquisition of active immunity after immunisation against diphtheria [3] and poliomyelitis.[4] It is important, therefore, to establish that all the components of a quadruple vaccine are effective at the age at which it is to be administered. Brown and Kendrick [5] have reported the results of administering quadruple vaccine to children aged 2–4 months. The response to the poliovaccine was poor, almost certainly owing to the presence, in most infants, of maternally transmitted antibodies. (The wise practice of immunising pregnant women with poliovaccine is increasing this problem.) It was also found that the response to the pertussis component was poor, 14 out of 43 children without antibodies failing to respond. Brown and Kendrick therefore advocate early immunisation with pertussis vaccine alone, this disease being especially severe under 1 year, and administration of a triple poliomyelitis, diphtheria, and tetanus prophylactic at about 1 year.

In an effort to overcome the poor response of young children, three main approaches have been tried: the inclusion of adjuvant, more and larger doses, and more concentrated vaccine. Quadruple vaccine with aluminium phosphate has lately been reported to be very effective in children under 6 months.[6] The prevalence of maternal antibodies was not very high in this series of children, and 83%, 80%, and 73% responded to poliovaccine of types 1, 2, and 3 respectively; but the geometric mean titres were low. In children over 6 months it was found that the response to poliovaccine in the quadruple vaccine was superior to the response to plain poliovaccine. The responses in children under 6 months were also good (over 85%) to the diphtheria, tetanus, and pertussis components. Perkins et al.,[7] who first noted the inhibiting

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2. *ibid.* Sept. 3, 1960, p. 531.
3. Barr, M., Glenny, A. T., Randall, K. J. *ibid.* 1950, i, 6.
4. Perkins, F. T., Yetts, R., Gaisford, W. *Brit. med. J.* 1958, ii, 68.
5. Brown, G. C., Kendrick, P. L. *Amer. J. publ. Hlth*, 1960, **50**, 1529.
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7. Perkins, F. T. Paper read at symposium on Stimulation of Antibody Production, British Society for Immunology, Nov. 25, 1960.

effect of passively transferred antibodies on the response to poliovaccine,[4] have devoted much effort to overcoming this difficulty. Although three doses proved superior to two doses, it was not until concentrated vaccine was used that satisfactory responses were obtained in children 1 week old. The concentrated vaccine (' Purivax ', Merck Sharp & Dohme) is very much more potent than vaccine now used in this country and elsewhere. Results obtained in Israel [8] with vaccine slightly more potent than the usual support the idea that children with maternally transmitted antibodies can be immunised with a potent poliovaccine. These results indicate that the goal of a satisfactory quadruple vaccine for use in the first weeks of life may be attainable; but the findings of Brown and Kendrick [5] show that the pertussis component may have to be modified. To give the fullest possible protection, pertussis vaccine must be given early in life; and it is known that the response, measured by agglutinin titre (not by a mouse protection test, which assays the antibodies concerned with protection [9]) is greater if an aluminium-phosphate adjuvant is used.

Living attenuated poliovaccine has also been found to be less effective early in life, but this has been ascribed to immunological immaturity rather than to the inhibiting effect of maternal antibodies.[10] This is unlikely to be overcome by a larger dose, since no antibodies appear despite multiplication of the virus in the alimentary tracts of the infants. Poliomyelitis being relatively rare under 1 year, it may be said that there is no reason to try and immunise children against it early in life. But such immunisation is desirable for three reasons: first, it is easier to persuade the parents to have the child immunised at that stage; secondly, poliomyelitis, when it does occur in neonates, is usually severe [11]; and thirdly, children should be immunised under cover of maternally acquired antibodies. If this is done, there should be no objection to incorporating an adjuvant in the vaccine.

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9. Medical Research Council report. *Brit. med. J.* 1956, ii, 454.
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THE FORTY-NINTH STAR

AMONG the United States of America (to which she has been elected this year) Alaska is likely to remain a nonesuch. The new State measures about 2000 miles between extremities with a population of less than a quarter of a million, or 1 person to 3 square miles. Of these, 38,000 are "natives" (Indians, Aleuts, and Eskimoes) and the rest " white " (which includes a few Negroes). Many of the whites are members of the Armed Forces on duty, and of the rest some are summer migrants from Seattle and San Francisco. Most of the population of all races live in scattered settlements on the coast or in the large river valleys. A large part of the country is virtually uninhabited. Some of the natives are still partially nomadic and live by the chase. There is a railway up country to Fairbanks, but boat and light aeroplane are the usual means of travelling. All these distinguish Alaska from the continental States, but the factor which gives it uniquity is its climate. A quarter of the new State lies within the Arctic circle, and the rest is as cold as charity for at least five months of the year. " Permafrost " is an ungainly word for the state of the ground which is frozen solid in summer as well as in winter a few feet below the surface, but it is a very awkward reality. It makes the supply of water and disposal of sewage equally difficult. When the surface layer thaws in the spring the water cannot seep away, and in summer most of the low country is a morass which breeds uncountable hordes of blood-thirsty insects. Travel even for a few miles is never easy, and in spring and autumn it is sometimes impossible. Quickly maturing crops such as lettuces grow luxuriantly in the summer, and there is some dairying and poultry-keeping.

In face of these difficulties a brave attempt has been made to offer the benefits of modern medicine to Alaskans of all races.[1] Legend had it that when the first Americans landed on these barren shores (the Russian sealers had preceded them by a hundred years) the Indians and Eskimoes enjoyed remarkably good health on a diet of fish and meat—often raw and flavoured with some wild herbs and berries. They did not suffer from scurvy (as the whalers did) but sometimes died of starvation. Nowadays most of the natives have developed a regrettable taste for crackers and doughnuts and live a life not much different from that of the immigrants. The crude death-rates, however, still show a figure for natives about twice that for whites, and for maternal and infantile deaths the difference is even greater. The death-rates for accidents and homicide are about twice those of the U.S.A. as a whole, and for alcoholism about six times. But, contrasting the figures for 1958 with those for 1950, the change is for the better in almost every instance. The reduction of the death-rate from tuberculosis from 175 to 12 per 100,000 is an outstanding triumph. Alaskan home life—especially in the winter—is conducive to cross-infection. Tuberculosis seems to have been introduced by the whites, and the natives were extremely susceptible. The number of hospital beds was quite insufficient, and the isolation of the communities often deferred diagnosis until it was too late. Now chemotherapy, a special allocation of funds from federal and territorial sources, and a determination to succeed have had their reward. As in more favoured lands there are empty beds in the tuberculosis hospitals.

Other infectious diseases take their toll. Enteric infections are common (as they are in the north of Europe) but do not seem to differ from those elsewhere.[2] Epidemic influenza occurs from time to time. It is a land where man lives close to his animals. *Echinococcus granulosus* and *E. multilocularis* occur together. Rabies is endemic among wild animals, but human infections are rare. The only disease which Alaska might claim as its own is a corneal scarring of unknown origin, which is a major affliction of the natives. There is obviously work enough to keep the four public-health laboratories occupied, but poor communications limit their usefulness. The distribution of scanty medical resources in a thinly populated country is a problem all the world over. In Alaska there are Government hospitals run by the Public Health Service and the Fish and Wildlife Service. There are community hospitals and hospitals run by religious bodies. Of 163 doctors, 117 are in private practice and most of these are in the larger cities on the south coast. In addition, the Armed Forces have their own medical service. To the outsider it seems a muddle, and likely to be even more of a muddle in this period of transition to Statehood. One of the successes of our reviled National Health Service has been in rationalising the use of our hospitals to provide the best service to the community without waste or overlapping of functions. If our colleagues in Alaska will not

1. *Publ. Hlth Rep., Wash.* 1960, **75**, 878.
2. *ibid.* p. 913.

regard the suggestion as too indelicate, we would think that some such overriding authority would be a great help in their proud and ambitious new State.

RENAL SEQUELÆ OF EPIDEMIC HÆMORRHAGIC FEVER

DURING the Korean campaign some 2000 cases of epidemic hæmorrhagic fever (E.H.F.) occurred among the United Nations' Forces. The clinical features of this disease are now well established.[1–11] Some renal involvement is so constant that the diagnosis is scarcely tenable in its absence. Albuminuria is found early and is commonly followed by a fall of urinary specific gravity and the appearance of blood and casts. In the more severe cases oliguria, anuria, and nitrogen retention develop, together usually with a period of hypotension. After the acute phase abnormal elements rapidly clear from the urine; and prompt restoration of renal function is the rule, although in some patients impaired urinary concentrating power persists for many months. The mortality of the disease is 3–5%.[7]

In fatal cases the kidneys contain striking lesions [12–16] of essentially "lower-nephron nephrosis" type.[17] A distinctive feature of the renal lesion is hæmorrhage in the junctional zone—an expression of the generalised capillary damage in E.H.F. There is extensive necrosis of tubular epithelium with gross rupture of many tubules. The nature of these lesions has been beautifully demonstrated by micro-dissection.[18]

In view of the sometimes-severe renal damage it is perhaps surprising that in the majority of cases renal function is restored fairly rapidly. Long-term follow-up of the widely dispersed survivors of this epidemic is difficult, but a survey of records and a limited clinical study have been carried out.[19] The medical records of 1416 U.S. Servicemen who had E.H.F. between January, 1951, and August, 1953, were examined. The majority recovered clinically within a few weeks of onset; but in 25% urinary concentrating power was not restored for eight weeks, and in 9% this was impaired for twelve or more weeks. The nature and frequency of subsequent hospital admissions (other than for follow-up) to the end of August, 1956, were analysed. In this period disease of the urinary tract had been diagnosed in 35 of the E.H.F. survivors—an incidence significantly greater than that among a suitable control series. Pyelonephritis was frequently diagnosed, although bacteriological proof was rarely obtained. The significance of these findings is uncertain, as a history of E.H.F. may somewhat prejudice subsequent clinical judgment. In 4 cases urinary concentration was impaired more than two years after the acute attack; and in 2 excretion of phenolsulphonphthalein was abnormal. There was no evidence of renal failure or of progressive disease. Hypertension was not encountered. A clinical study of a partly selected group of 15 survivors of severe or moderate E.H.F. yielded evidence of mild defects of renal function after intervals of up to four years, impairment of tubular function being greater than concomitant reduction of glomerular filtration. These findings, which cannot be due to loss of complete nephron units, perhaps indicate imperfect regeneration of specialised tubular epithelium. Continued improvement appears possible for several years.

This work casts light on the residual renal damage after E.H.F. and emphasises the essentially good prognosis for the majority of patients. The few who do not recover completely suffer a minor loss of renal reserve probably compatible with normal duration of life. Similar recovery of function is found after acute renal failure from other causes, although the initial mortality is much higher than in E.H.F.[20 21] Whether residual damage resulting from this disease will predispose to the development of hypertension is still uncertain.

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12. Hullinghorst, R. L., Steer, A. *Ann. intern. Med.* 1953, **38**, 77.
13. Kessler, W. H. *ibid.* p. 73.
14. Lukes, R. J. *Amer. J. Med.* 1954, **16**, 639.
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21. Finkenstaedt, J. T., Merrill, J. P. *New Engl. J. Med.* 1956, **254**, 1023.
22. See, for example, *Lancet*, 1957, ii, 935, 995, 1053.

CHINESE VIEW

REPRESENTING the Chinese Medical Association, six Chinese doctors have been spending a few weeks in this country at the invitation of the Royal College of Physicians of London. As three of them work at the Chinese Academy of Medical Sciences in Peking, and two others hold chairs in Shanghai, their interest has been mainly in scientific developments, and outside the London area visits have been paid to Edinburgh, Glasgow, Oxford, Cambridge, Liverpool, and Newcastle.

Having thus seen something of British research, especially in their own subjects, the delegation offered in return to give some account of developments in their own country, and on Dec. 12 Dr. Hsueh Kung-Chuo, vice-president of the Academy, gave a lecture at the London School of Hygiene and Tropical Medicine. What he said about the control of epidemic diseases and the remarkable advance of public health was familiar to some of his hearers from the reports of Western doctors who have visited the People's Republic [22]; but all must have been freshly impressed by his emphasis on the advantages of fusing Western and traditional methods of medicine—a policy which Communist leadership has increasingly urged on the Western-trained profession in China. Mention was made of "combined" methods of treatment, including traditional methods such as acupuncture, cupping, and breathing exercises, which are said to have given good results in chronic conditions such as hypertension and diabetes, and of regimes by which the majority of patients with appendicitis, cholelithiasis, and other conditions can be spared operation. On these matters we await further evidence with interest but with the cautious scepticism which is necessary for arriving at truth. Continuing scientific advance depends on dispassionate weighing of evidence, and the Chinese have yet to show that this is compatible with political leadership. Application of known facts is one thing but discovery of new ones is quite another.

Points of View

PER ARDUA AD ARDUA

D. M. McCLURE
M.B. Glasg.

" The shades of night were falling fast,
as through an Alpine village passed
a youth who bore 'mid snow and ice,
a banner with the strange device
'Excelsior!' "

SCIENTIFIC progress is the watchword of our times. Not only does the momentum of our advance increase daily, but every fresh piece of recorded data is seen as a further step towards a clearly defined goal, the attainment of which is only a matter of time.

This is best shown perhaps in the attitude of the layman to the " cure for cancer ". There can be few of us who have not been asked: " But surely doctor, it's bound to come, isn't it? . . . I mean, look at the amount of work that is being done!" To which one might reply that certainly the amount of investigation is vastly greater than ever before; that the tools of research are of ever-increasing complexity and scope, and that in every medical library, the very walls are bulging with the growing masses of undigested and indigestible data.

My present concern, however, is with more general considerations, and I shall comment on our failures to date in comprehending the vital processes of the cell (of which neoplasia is only one facet), and on the significance of the flood of medical literature which is overwhelming us all. In doing so, I would justify my apparent temerity by pointing out that the climbers on the highest pinnacles of the mountain of knowledge can be best observed from a position on its lower slopes.

* * *

In his first days as a student, the aspiring doctor is introduced to *Amœba proteus*, and is invited to philosophise on the imponderable mysteries of life locked away in this minute particle of protoplasm, as seen by " the eye which has a mind behind it ". In later years, however, when we come to deal with countless millions of cells, enormously varied in structure and function, and linked in a dynamic equilibrium to form the living human body, there seems to be no limit to the degree to which we presume to comprehend the most fundamental of their vital functions.

It is of course a basic human weakness, that we are unwilling to face any facts the recognition of which would be detrimental to our self-esteem; and we instinctively oppose any suggestion that there are limitations to the powers of the human intellect. We have no illusions concerning our other physical capacities: there are too many proofs in Nature of attributes superior to ours in muscular strength, acuity of eyesight, and so forth. But man owes his ascendancy to his brain, and we are notably reluctant to admit any bounds to our capacities in this respect. Today, however, we are having this recognition forced upon us.

The limitations relevant to our subject are those of our perceptive faculties, and I need specify only two. The first is our extremely limited power of instantaneous perception of number (readily shown by determining for how many black dots on a white card one can give the total number at a glance without individual enumeration), and the second is the fact that we have no sensory mechanism for appreciating, quantitatively, the interplay of forces maintaining an unstable equilibrium. Our limited perception of number virtually ceases to exist when we are confronted with a group of similar units in constant random movement: even the most mathematical of us cannot count a flock of sheep on the move, and the exasperated cry of " Stand still for a moment can't you!" is familiar to all who undertake the management of children. For an illustration of my second point, one may observe that the feats of the equilibrist and juggler are the result of years of reflex conditioning, and that the control he exercises does not derive from any quantitative judgment of the bearings and intensities of the forces he manipulates.

* * *

Before relating these points to the investigation of the living cell, one might profitably glance at events since the time of Virchow. In the first three-quarters of the century which has elapsed, the improvement of the microscope, and of the techniques of tissue processing, sectioning, and staining, created the science of " classical " morbid histology. The potentialities of this were so vast that years of continuous progress passed before any boundaries to them became apparent through developments in biochemistry and an increasing appreciation of cellular dynamics. By that time, a picture of disease processes in terms of hæmatoxylin and eosin was no longer enough. In microscopy, too, optical limitations had become increasingly obtrusive; nor were these adequately overcome by ventures into the ultraviolet. There was thus a general frustration, with the conviction that the most vital information lay just beyond the utmost limits then available of magnification and resolution.

Since then, however, the whole picture has changed, and a host of new developments in instrumentation has been showered on us—phase contrast, electrophoresis, chromatography, freeze drying, spectrophotometry, radioisotopes, the ultracentrifuge, interference microscopy, and, most spectacular of all, the electron microscope. One might well suppose that, with these formidable reinforcements, the remaining obstacles could be swept aside with ease, and that final understanding was at last within our grasp; but the results to date suggest that this is hardly so.

Let us consider for a moment some reports on the electron microscopy of biological materials, and particularly their verbal presentation—as, for example, in the study of blood platelets.[1] Phrases such as these are typical:

" There was a suggestion of a doubled external limiting membrane " . . . " Such vacuoles may represent organelles, or they may be holes . . . a part of their structure, or possibly artifact " . . . " The outer membrane seems to be 'feathery' " . . . " The release of 'clear bubbles' from the platelets is one of the first changes during coagulation ".

Or in the case of the leucocytes [2]:

" Fine dustlike grayish opacities make up the cytoplasmic background " . . . " The dense zone may be round, ovoid or bar shaped " . . . " Some of the granules of the eosinophils are of irregular outline " . . . " Poorly defined grayish densities ".

And let us not omit the human spermatozoon [3]:

" Two vacuoles containing partially opaque material " . . .

1. Hutter, R. V. P. *Amer. J. clin. Path.* 1957, **28**, 447.
2. Rinehart, J. F. *ibid.* 1955, **25**, 605.
3. Rothschild, Lord. *Brit. med. J.* 1958, i, 301.

"a remarkable structure . . . somewhat reminiscent of vertebræ" . . . "A fibrillar sheath which may or may not be spiral".

It would, one feels, be something of an overstatement to describe any of these observations as a blinding revelation of ultimate truth, and in the similar application of phase contrast [4] the same descriptive terms abound:

"Angular blocks of heterochromatin" . . . "Highly refractile specific granules" . . . "Large dark ellipsoid mitochondria."

In every instance we are dealing with verbal renderings of visual impressions of structural entities, whose functional significance cannot be assessed by any process of inspection; and, even where an attempt is made to study an active vital process, as in bacterial cell division,[5] we read that "the impression is gained that before actual division, there are deep lying processes going on, for the bacteria become suddenly restless, and have continuous changes of form"—a description which certainly conveys the sense of activity but tells us nothing of the mechanisms involved.

Indeed, so far from bringing us nearer to complete understanding of cellular function, these advances in microscopy seem to emphasise the presence of barriers to our further comprehension, by revealing structural complexities and minutiæ whose role cannot be interpreted by visual inspection. This, however, is hardly surprising, since the ultimate goal of our search lies in a dynamic equilibrium of the utmost complexity, maintained by an interplay of forces whose analysis is beyond the scope of our sensory receptors. One has only to glance at a living leucocyte by phase contrast to appreciate the self-deception in which we indulge by our descriptions of the shrunken and artificially pigmented remains of similar cells—a deception which we foster by the titles and eponyms which have so long served to cloak our ignorance. One can imagine an attempt to describe in similar phraseology the components of a watch, by someone with no knowledge of their purpose: the main and hair springs might be termed the "greater and lesser spiral filaments", the jewels the "rubroid bodies", and the regulator could well become "the digitate organ of Pflugelheimer"!

In trying to interpret the functional roles of intracellular particles by observing the living cell, the position of the microscopist can be likened to that of a man from Mars in his flying saucer, viewing a series of football matches. This comparison is by no means too fanciful, if one considers such a viewpoint in cytological terms:

"An ovoid area, with a broad peripheral zone of densely packed identical particles, exhibiting a trace of Brownian movement, and throughout which radial striations appear with varying degrees of clarity. Within this there is a clear central area, in which a strikingly constant linear pattern is displayed, and throughout which a small number of particulate bodies show active and apparently random motility. Well-defined chromatic differentiation is commonly shown by these, though this is not invariable, and continued observation shows a frequent tendency for these bodies to form temporary aggregates at one or other polar extremity of this central area. Certain observers have reported the presence in this zone of a much smaller single particle moving at very high speeds, and further confirmation of this point is awaited . . ."

It is on the whole rather doubtful whether our Martian observer will, in time, be able to interpret the niceties of the offside rule, and I suggest that our own view of the living cell is equally disadvantageous in respect of the visual interpretation of functional activities.

* * *

At this stage then, one is compelled to admit that to see is not necessarily to comprehend, and our hopes that these new techniques would provide the answers have not been realised. There is, too, a further fallacy in our approach to the relationship of cellular structure and function. In dealing with the whole organism, we are able to consider organs and systems as separate entities, and thus we can study the heart and circulation without any direct correlation with, for example, gastrointestinal function; but when we consider any individual intracellular body we find ourselves in a realm where the function of any single component can only be expressed by its dynamic relationship in terms of molecular equilibrium with each and every other constituent entity of the cellular protoplasm. It is this fact which confronts us squarely with those fundamental limitations in our powers of perception and comprehension to which I have already referred. Nor does it avail us to invoke the aid of chemistry; for we have already reached the point at which chemistry and physics lose the last trace of any separate identity, and beyond which we have to discard the alphabetical symbols by which we are accustomed to represent molecular structure. The human intellect cannot bridge the gap between the representation of chemical structure by arbitrary symbols, and the comprehension of the reality of matter in dynamic terms of fundamental particles; nor are we much aided in this by molecular models of coloured plastic balls. These are still static symbols, and the essential fact which we so readily forget is that each individual chemical atomic symbol represents in itself a dynamic entity of particles whose true nature is unknown to us, involving as they do the ultimate mystery of the "emptiness" of matter. The position becomes ludicrous when we use such symbols to build up a structural picture with spatial relationships so complex that we cannot retain a coherent mental picture of them—as in our diagrams and models of the molecular structure of aminoacids and proteins. In our preoccupation with the configuration of such molecules, we forget that the basis of vital activity lies not in patterns of spatial relationships but in the forces which maintain or alter these relationships; and when we view the living cell, we are all too ready to regard the activity of the protoplasmic particles as a hindrance to detailed study, whereas it is in the balance of these forces that the ultimate truth resides.

You may wish to remind me that in enzyme chemistry, serology, and histochemistry there is a large body of workers whose efforts are also directed to matters of vital dynamics; and I hasten to acknowledge my awareness of their activities. But they too suffer in the pitfalls of attempting to equate dynamic processes with static symbols. In the nevernever land where every factor has a co-factor, every enzyme a co-enzyme, every active principle an inactive precursor, and all are surrounded by potentiators, inhibitors, and accelerators, lavishly endowed with stable and labile fractions, nothing is quite so elusive as the factor which "has still to be isolated in a pure form". It may be pertinent to comment that one may observe and measure the resultant of a complex of forces, but that this resultant cannot exist independently of the forces which give rise to it. Again, the problems which beset these workers have some affinity with those

4. Discombe, G. *Acta hæmat.* 1950, **3**, 151. (Abstr. Year Book of Pathology and Clinical Pathology. Chicago, 1950.)
5. Haselmann, H., Kappel, W. *Arch. Derm. Syph., Wien.* 1949, **187**, 501. (Abstr. Year Book of Pathology and Clinical Pathology. Chicago, 1949.)

of a child attempting to pick up a globule of mercury: it keeps on dividing into smaller globules of varying size which can be reconstituted into the original one; and, moreover, the number and size of these fractions is not constant from one attempt to the next. This may well have some bearing on the familiar type of statement to the effect that " the co-factor R, hitherto regarded as identical with the sub-fraction XI, has now been shown to differ in the possession of a thermolabile constituent associated with the α_2-globulin ". All of which simply emphasises the fact that in dealing with entities for which the conventional symbols of chemistry are invalid, the substitution of arbitrary titles for a variety of intangibles solves nothing, and one might pose the question: " Given any two points A and B on a linear graph, how many intermediate points can be plotted?"

It follows therefore that any understanding of these matters must be sought not in symbols of chemistry but of mathematics—in which we must include the fourth dimension of time. The problem here is that we cannot begin to look for it without quantitative physical data on the fundamental particles of matter participating in cellular function; yet when we venture to derive such data from living protoplasm, we find ourselves without any fixed point of reference to which we may relate our measurements. Furthermore, when a single molecule of protein can involve complexities exceeding our faculties of comprehension, how do we presume to proceed to the full understanding of the complex of forces binding the millions of molecules in the cell, and thereafter to the balance of forces throughout the millions of such cells in the whole organism?

The answer is, I fear, that we cannot. In considering an entity of almost infinitely complex relationships, the simultaneous comprehension of the whole and the relationship of each constituent part to every other is not within the capacity of the human mind. And one of the principal causes of the current deluge of medical and allied scientific literature is the fact that when the biological investigator reaches the point of being unable to see the wood for the trees, he is all too ready to attempt to resolve his difficulties by embarking on the study of individual leaves!

* * *

Having made this point then, I must offer an answer to the question implied in my opening paragraph: Is it true that, in our scientific " progress ", we are moving steadily towards an attainable goal; and, if not, what is the significance of the ever-increasing activity in research? The answer to the first part is an unequivocal " No ", and the reason lies in the answer to the second part. As a first step to providing this, I would quote an analogy from Florey's *General Pathology*.[6] In referring to the difficulties of interpreting functional disorder from tissue sections, he comments: " It is as if a full length cinema film were taken, every two hundredth frame extracted, the extracted frames jumbled together, and an observer was then asked to reconstruct the story of the film from them ". By a simple extension this analogy can provide a comprehensive and convincing answer to our question.

Let us consider the course of events if, instead of seeing a new film in the normal way, every press critic were presented with the full thousand yards or so of celluloid strip, with a hand lens, and were instructed to extract the maximum amount of information from its study, frame by frame, and in doing so, to compare notes regularly with all the others similarly engaged. It would be immediately apparent whether the film was in a modern or a " period " setting, or whether it dealt with Naval warfare, " Western " adventure, or " Big City " life. On these preliminaries, there would be uniform agreement. The next step however, would be to identify the actors, and here disagreement would soon be apparent—even concerning the stars.

That however is only a beginning. Next there would be the evaluation of the plot and characters of the film, and here the observers would enter a realm of pure speculation. Certain identifying features would of course appear at times, but usually the inspection of consecutive frames would give little insight into the human relationships being depicted. Nevertheless, our observers would evolve various hypotheses based on their scrutiny, and argument would revolve around these. At a later stage, occasional facets of detail would be picked out which would compel the abandonment of views which had been generally accepted:

" The observation by Snooks (1959) that the Vauxhall car in frames 6026 to 6618 is a 1954 model, and not a 1953 model, reopens the question of the identity of its driver, as A . . . B . . . the actor believed to have taken this part died in March of the latter year ".

And so it would go—the scope for speculation and argument would expand continually, with the scrutiny of ever more minute features of detail—even to the point whether the date on the second tombstone on the left was 1864 or 1866. And of course, special investigations might rear their heads. " A review by model, date, and registration number of cars and motorcycles appearing in street scenes ", by Tweedledum A. and Tweedledee B. (A.A. and R.A.C. research scholars), might well be followed by " A critical evaluation of certain anomalies and discrepancies in continuity, with special reference to anachronisms ". The extraction of factual data would be virtually endless; but, even when every scrap of the information thus acquired had been assembled, two vital points would remain unanswered and unanswerable—the quality of the acting performances, and the entertainment value of the film!

* * *

And now perhaps the application of the analogy to the current mass of medical publication is clear—namely, that the vast majority of all articles and studies on cellular function are similarly devoted to the minutiæ of static and background detail, wholly divorced from the dynamics of life itself. Our general failure to appreciate this derives, I suggest, from the fact that whereas in the film analogy the successive frames represent only two-dimensional images of three-dimensional subjects, our biological specimens are three-dimensional entities, accessible to laboratory processes. What we overlook is that in taking our samples we are removing them from their proper context of vital activity in both space and time, and that the steps to which we subject them correspond to cutting out the film-strip figures with scissors, or to scraping off the emulsion, as a preliminary to closer individual scrutiny. (When a writer on cellular respiration [7] refers to " properly isolated mitochondria " one is not altogether clear as to the precise criteria of propriety in this matter; but presumably they approximate to those applicable to a properly eviscerated viscus!) There is, too, a further

6. Florey, H. W. General Pathology; p. 10. London, 1958.

7. Glazer, A. N. *Advanc. Sci. Lond.* 1956, **12**, 398.

point on which we would do well to ponder namely, that, so far as our senses are concerned, the only way in which the particles of cellular protoplasm can impinge on these is as retinal stimuli. We stand in the same relationship to these particles as does the astronomer to the uttermost stars, and at either extreme we see through a glass darkly.

* * *

What conclusions may one presume to offer? In the first place, I think we should emphasise the distinction between the accumulation of data and the advancement of knowledge. The assimilation of a mass of information is a process which can only be carried out by the individual; and his capacities are limited not merely by considerations of intellect but also by the need to spend part of each twenty-four hours in sleep, and ultimately by the span of life itself. One does not need to be a Montgomery to appreciate that, in a military campaign, advance without consolidation spells ultimate disaster from breakdown in the lines of communication; and in medical science the point at which the breaking strain is developing is in the impossible task of incorporating the essentials of a growing mass of increasingly specialised knowledge in the basic education of the student. Indeed, the position of the student today—which includes us all—resembles that of a solitary diner confronted with the products of a thousand chefs, all simultaneously engaged in producing a continuous succession of culinary masterpieces!

Quite apart from the sheer quantity of information, there is the even more important matter that, in our zeal for continuous advance on every front, we are failing to give adequate thought to our ultimate aims. If one were to pose the question as to what in fact is our ultimate goal, the general answer would undoubtedly be " the conquest of disease ". Having made this reply, however, few will trouble to think further about the practical implications of their statement (which is widely used: indeed the claim is often made that certain diseases have already been overcome). To do so, we must first define the most fundamental duty of the doctor. If, again, the public were invited to specify this, the majority would almost certainly give it as " the preservation of human life " and in this, surely, lies a basic error.

One recognises of course that current emphasis is directed to " positive health " rather than to awaiting the appearance of disease; and this is eminently proper during that greater part of the normal lifetime in which the attainment of health is a practical possibility. Ultimately, however, the doctor encounters circumstances—terminal carcinomatosis, senility with bedsores and incontinence, and other comparable states—in which not only has the attainability of " positive health " vanished for ever but the preservation of life itself is equally impossible. But he still has his most fundamental duty which is the relief of suffering, in which his obligations are not discharged until life is extinct. In our constant probing into the cell, therefore, we must bear in mind that however vast an array of established fact we acquire, this knowledge will never ensure the perpetual continuity of function of any living organism; and it should be clear that our much-vaunted goal of the " conquest of disease " calls for some more searching analysis.

A fact to which we are all too ready to turn a blind eye is the ultimate inevitablity of death; and in practice we reach a point where our efforts to overcome disease merge into a futile attempt to postpone death in circumstances where its physical processes are irreversibly established. It is true of course that, in the life of any individual, medical intervention may avert repeated dangers, any one of which could have been fatal; but there is no such thing as the conquest of disease. The position is directly comparable to the efforts of the Dutch in keeping the sea at bay. Their dykes are erected, strengthened, and extended. Now and again a collapse occurs, with inroads of flooding, in response to which resources are marshalled and the breach is repaired; but continued safety is achieved only by constant vigilance and structural maintenance. The ocean is always there, and there is no end to the processes of gradual erosion and the searching out of weak points in the defences; nor is time of any account to the sea. The same is true of disease in all its aspects. There is no escape from the fundamental truth that we must all die, and that some will die sooner than others. This is an unalterable fact. Were it otherwise, we would have to contemplate a situation in which the human body would attain a state paralleling that of the " wonderful one-hoss shay " of Oliver Wendell Holmes, in which, as you will recall, the structural materials were of such superlative excellence that no single component wore out before another, so that in the final issue there was no localised mechanical breakdown, but a single synchronous cataclysmic collapse of everything. No-one could regard this as an attainable, or even a desirable, ideal; and one might ask whether, in many of our efforts to lessen man's vulnerability, we are not engaging in a vain attempt to deny his mortality—the more so at the present time, as a glance at the standard tables of life expectancy will show that our current average is approaching the Biblical limit of three score and ten, a circumstance in which the linear graph of the effort and cost per unit of further progress describes a curve which is now climbing almost vertically.

* * *

At this point the reader who has borne with me thus far may wish to pose a final question: " If I am suggesting that in our efforts to comprehend the living cell, most of our activities amount to beating our heads against a brick wall while uttering happy cries, how do I reconcile this with the undeniable fact of the enormous and increasing expansion of every branch of science?"

I have already exceeded my quota of analogies; but to answer this, I ask indulgence for one more. If we can picture the individual molecules of a soap bubble as sentient entities, then we have this situation. While the bubble is being blown, they would be aware of two factors: first, a gradual movement radially, steadily increasing their distance from the centre of the sphere, and secondly an increasing peripheral tension between them and their immediately contiguous neighbours at all points —a force imposing a progressive limitation on their range of local movement. At the bursting of the bubble, however, and in the microseconds immediately thereafter, the first impact of the event on their consciousness could only be by their awareness of a tremendous surge of acceleration upwards and outwards, far exceeding anything in their previous experience, and coupled with a sudden release from the restrictive peripheral tension to which they had previously been subjected.

With this in mind then, let us extend our time-scale of microseconds to decades, and substitute for the image of the bursting bubble the pattern of events in medical

science in the present century. The parallel must, I feel, be clear; but for added emphasis, it can readily be developed. The next stage as the pattern unfolds is that of our initial exhilaration becoming progressively tempered by the consciousness that the Science of Medicine is no longer a coherent and unified structure, but a series of isolated bodies without intercommunication or co-ordination, which are becoming more and more widely separated; and then by the increasingly disquieting realisation that in our own particular unit, while our speed continues undiminished, not only do we have no effective control over its degree or direction, but there is no sign of any ultimate point of arrival.

In the midst of all that we choose to call progress, therefore, it might repay us to reflect that there is no such thing in Nature as a structure—material or social—which is capable of perpetual expansion; and in the advancement of knowledge the ultimate limiting factor is the fact that in each succeeding generation the newborn infant arrives without any legacy of the accumulated knowledge and experience of its parents. Before the summits attained by the latter can be surpassed, the ascent must be repeated by their successors.

* * *

As to the future, I have already presumed too much in the role of prophet; but I would venture one comment. I began by referring to the general attitude towards the "cure for cancer", which of course is only one facet of the ever-increasing demand for miracle drugs". Surveying the contemporary scene, one cannot but feel that instead of relying on an endless flow of polysyllabic organic pharmaceuticals, we should be better equipped for the years ahead by a philosophy of life which would enable us to recognise and accept our limited tenure of existence, and in doing so, to face its end 'th dignity and courage. This was not lacking in bygone generations, and, as the progress of Nature tends to move in cycles, we may, in time, find ourselves guided towards its rediscovery.

Conference

ACCIDENT SURGERY

A CONFERENCE on accident surgery was held in the Royal Faculty of Physicians and Surgeons of Glasgow on Nov. 30 to Dec. 2.

Causes and Treatment

Mr. WILLIAM GISSANE said that the usual cause of injury, very rapid deceleration, had been studied in the United States Air Force on jet-propelled sledges which were decelerated from 150 to 34 m.p.h. per hour in $^1/_4$ second, which produced a force of 46·2*g* and 8000 lb. load on the harness.

If such a force was not to be fatal, it had to be applied over a wide area and not too rapidly. Safety-straps must include the shoulders, especially for front-seat passengers. The accident-rate per 1000 vehicles on the road was falling, but the total accident-rate was rising steadily and would reach 500,000 injuries per year in the near future. Mr. Gissane compared the administrative cost of motor insurance (£23 million) with the cost of treatment (£11 million), figures that indicated a false sense of values. He made a plea for the segregation of slow-moving traffic from fast vehicles.

Mr. WILLIAM SILLAR described the chest injury as a challenge to modern surgeons which had not yet been adequately answered. The points which told against the patient with chest injury included obstructed airway, hæmorrhage, sucking wound, tension pneumothorax, tamponade, mediastinal emphysema, and paradoxical movement. Mr. Sillar was disappointed by the patient-triggered respirator: an intermittent positive-pressure respirator was proving better. He advocated fusion of the chest segment, either by traction with 'Cellophane'-covered flex or by fixation by a Kirschner wire. Anterior-segment injuries were the most severe, and some of them could be dealt with by plating of the sternum.

Discussing the management of the unconscious patient Mr. JOSEPH SCHORSTEIN pointed out that unconsciousness varied from slight concussion to antemortem coma. Even slight cerebral œdema might lead to increased intracranial pressure and eventually to coning through the tentorium. A comatose patient should not be nursed on his back, but with the foot of the bed elevated. The mouth and pharynx should be aspirated frequently, and physiotherapy used to prevent chest complications. It might be possible to deal with respiratory obstruction by endotracheal tube, but only for 24 hours. The indications for tracheostomy were failure of pharyngeal suction, injuries and infections of the chest, and other injuries which prevented frequent change of position.

Reactions to Injury

Speaking of the metabolic reaction to injury, Prof. THOMAS SYMINGTON said that "traumatic inflammation" was now recognised as an endocrine response of the pituitary-adrenal axis; and he described the post-traumatic response of the adrenal and the secretion of steroid hormones. Aldosterone was also produced in shock. The negative nitrogen and potassium balance found after injury might be due to starvation, low intake of water, or immobility. In fat-embolism there might also be an endocrine factor, a fat-liberating hormone.

Reviewing the biochemical problem of traumatic oliguria, Dr. J. W. CHAMPERS stated that oliguria was a normal reaction to injury and the urine output might fall to 500 ml. per day. When severe oliguria developed, it was usually associated with tubular necrosis. Post-traumatic kidney change was often associated with severe and prolonged oliguria. Hypotension might be the only cause of the kidney change, but toxæmia was also involved in injury during pregnancy. Pure toxic effects were seen in carbon-tetrachloride and mercuric-chloride poisoning. The symptoms of acute renal failure included anorexia, nausea and vomiting, diarrhœa, drowsiness and restlessness, tachycardia, hypertension, leucocytosis, anæmia, tendency to bleed, and defects of healing. The condition might be avoided by planned and adequate transfusion or by correction of depletions.

Dr. A. C. KENNEDY divided the treatment of acute renal failure into prophylaxis, conservative management, treatment in the diuretic phase, and use of the artificial kidney. Prophylaxis was summed up in the control of hæmorrhage, the restoration of blood-volume and blood-pressure, the prompt removal of damaged tissues, and the control of infection. Rational conservative therapy was introduced by Bull and others, and in modern modifications of the regimen the daily volume of fluid was 400 ml. Carbohydrate was now given to spare 50% of protein breakdown—about 100 g. per day.

Burns

Mr. IAN MCGREGOR divided the damage in the acute phase of burns into skin damage and capillary damage. There were three degrees of capillary damage: capillary leak; stasis and hæmoconcentration (this stage was irreversible and necrosis would follow); and coagulation. Erythrocytes were always injured, and hæmoglobinuria might be produced. In a 50% burn, 12% of the red cells might be destroyed. The capillary

leak was greatest in the first 8 hours and ceased at 48 hours. Replacement should also follow this rate of flow. In general, a burn of the adult below 15% and of the child below 10% did not require transfusion, but prevention of shock was better than treatment. Mr. McGregor preferred plasma as transfusion fluid, though occasionally whole blood was required for the extensive deep burn, after hæmoconcentration had been corrected, or electrolytes when oral intake was insufficient. There was no satisfactory dose formula, and the clinical state should control dosage. The first two pints could be given rapidly. The clinical criteria were pulse-rate, packed-cell volume, peripheral circulation, thirst, and urine output (50 ml. per hour in the adult).

Shock should be corrected before treating the burn. Cleansing should be by detergent (e.g., 1% cetrimide) and blister skin should be removed. The method which most efficiently kept the burn dry should be used, so that dressing might be needed for one site and exposure for another (the hand should be dressed and the face and perineum exposed). The actual dressing was not important but should be adequate in extent and depth, and it needed fixation.

Speaking on the late phase of burns Mr. THOMAS GIBSON said this phase only arose in deep burns. The problems were infection, protein loss, and anæmia: all were aggravated by a raw area and grafting solved them, but these factors did not favour skin grafts. The burn slough could be treated by immediate or delayed excision, or be allowed to separate spontaneously. Excision should go down to deep fascia. Delayed excision might start hæmorrhage. Spontaneous separation took more than three weeks. The infecting organisms were the streptococcus, which killed grafts, *Pseudomonas pyocanea*, which produced a toxin, and the staphylococcus, which was becoming more important in burns. Protein loss might be partially prevented by gastric-tube feeding with protein or by intravenous albumin or plasma. Homografts from mother or from brothers or sisters to the patient did better than from the father, but the advantage of long survival must be balanced against the disadvantages. Cadaver skin might be used when it becomes legal to do so.

Traumatic Ischæmia

Mr. GEORGE SMITH said that ischæmia of muscle might be seen early after an injury but was recoverable up to 12 hours. Later colliquative necrosis ensued, and little good could result from attempts to restore the blood-supply. Early exploration was justified, and repair might be by end-to-end suture, by lateral arteriorrhaphy, or by grafting. Vein grafts were favoured for small vessels and 'Teflon' for prostheses.

Head Injuries

Mr. G. F. ROWBOTHAM said that the indications for operation in head injuries might be early (immediate or within 48 hours); intermediate (2–28 days); or late (after 28 days). Early indications were anoxia, shock, loss of blood, compression of the brain, and compounding. Intermediate operation was indicated by infection, increased intracranial pressure, and irritation. Late operation was undertaken for chronic signs of head injury, epilepsy, bone defects, aneurysm, or nerve palsy. Cerebral anoxia (possibly due to chest injury or inhaled vomitus) must first be treated. Diagnosis should then be attempted and physiological therapy undertaken—replacing blood-loss, adjusting fluid and electrolyte balance, and ensuring adequate nutrition. If surgery was required, definitive surgery should be done at the first operation.

Visceral Injuries

Prof. W. A. MACKEY said that visceral injuries were hard to classify because of coexistent lesions. The liver was the organ most commonly damaged, then the spleen and the kidney. The danger of damage to solid viscera was hæmorrhage; to hollow viscera, infection. Treatment should include restoration of the airway and pulmonary function, control of hæmorrhage, stabilisation of major fractures, and closure of alimenatary defects. A large incision was necessary. Ileus should be treated by intragastric Levine tube and intravenous fluids to control the electrolytes.

Orthopædic Problems

Mr. E. A. NICOLL, in an account of fractures of the upper tibia, dealt first with the cause, prevention, and treatment of stiffness of the knee. The cause was often œdema and no unnecessary immobilisation should be allowed. Fracture of the tibial plateau might be difficult if the paracondyle gutters were affected, but the collateral ligaments were rarely involved and united readily; the classical plateau fracture depended on intact ligaments, instability being due to loss of the plateau and not to ligament injury. Fracture of the tibial spine was an avulsion fracture and should be reduced. Mr. Nicoll described the treatment of stiffness, avoiding passive movement and movement against resistance until the last stage. If there was no improvement for three months, quadricepsplasty was advised, loosening the adherent rectus femoris, cutting paracondylar and intra-articular adhesions, and correcting the shortened rectus. In 17 cases described, improvement had ranged from 30° to 100°.

Prof. ROLAND EARNES discussed fractures of the cervical spine. The commonest sites of injury were at the upper and lower ends, cord injuries being commonest at C5, 6, and 7. The mechanism of injury might be compression, flexion and rotation, or hyperextension. Proprioceptive sensation was sometimes still preserved when the sensory functions were lost; and this was a good prognostic sign. Treatment should be skull traction in the axis of the cervical spine, using Cone's callipers. When the facets were clear, traction was reduced from about 30 lb. to 5 lb. and the spines were fused by a cancellous graft. Laminectomy or removal of the articular facet was sometimes necessary. Hyperextension injury was usually found in the old. It was due to bulging of the interlaminar ligaments and produced a similar lesion to that of a prolapsed disc. Treatment was rest in bed, avoiding extension.

In the clean incised wound with section of the nerve, Mr. ARTHOL PARKES favoured primary suture, avoiding axial disorientation. He thought that muscle changes were minimised by early suture and that fibrosis might be reduced. In the closed nerve injury, a waiting policy was probably justified, but nerve regeneration took a long time.

Accident Services

Mr. ROBERT WRIGHT thought that our present accident service was poor and outlined the requirements of a good service. The main accident centres should be few and should have access to a specialist panel. The smaller hospitals might receive patients back from the main centre for nursing after definitive treatment had been completed. Staffing should be adequate to allow rest periods and refresher courses. An orthopædic surgeon would be required but would not necessarily be in charge. Training of students and general practitioners was required, but no doctor under the rank of senior house-officer should be on the staff of an accident centre. Registrars from general surgery should spend six months of their training in an accident post. A career accident surgeon should train in all the specialties.

Dr. CYRIL BAINBRIDGE, senior administrative medical officer of the Western Regional Hospital Board, noted the rise in outpatient attendance, many of them accidents. The cost of the National Health Service in Scotland had risen from £26 million in 1949 to £52 million in 1959, and the community was entitled to expect better casualty services than it got. There should be fewer but better accident centres, though local opposition could be expected to the closure of small units. Probably one good accident centre was needed for each 200,000 population; it should have a burns unit, directed by a traumatic surgeon.

Very Special Articles

NORMALCY AND THE GAMMA EFFERENT SYSTEM

JOHN H. MENKES
M.D. John Hopkins

"No judgment can rightly be formed either of my method or of the discoveries to which it leads . . ."—F. BACON, *Novum Organum.*

THE social, political, and economic upheavals of the past two decades have been a great strain upon the central nervous system of man, and upon its ability to adapt to the daily stresses to which it is subjected.[1]

Recent experiments demonstrating that only the normal organism is capable of withstanding the slings and arrows of outrageous fortune [2] have placed a premium upon the normal man, and have led to attempts at defining the variables that circumscribe such a biological system.

That a neurophysiological viewpoint might help with this vital problem was already postulated by Freud, who early in his career predicted that at some future time physiological data and concepts would be substituted for psychological ones. *Es ist doch Alles Eins!*, he is said to have remarked after the famous Kitzbühel Conference in 1913 on the eve of the Great War.[3]

But in order to approach this problem in a purposeful fashion we must first assay a definition of normalcy. "For every stimulus the correct response" is a dictum first announced by Jeremy Bentham,[4] and one which is as true today as it was 120 years ago. Proceeding from this definition we find that it is the incorrect response to a stimulus —many examples, too numerous to cite at this point, might be given—that distinguishes the abnormal individual and marks him an easy prey to environmental stresses. Of equal importance is the speed of reaction, both accelerated and inhibited responses being equally pathological.[5]

TOUCH AND HEARING

While there are many types of receptors—exteroceptors, enteroceptors, proprioceptors, just to name a few —we will by choice concentrate on two systems which, according to Harry Stack Sullivan, are paramount in determining interpersonal relationships—namely, touch and hearing. It is through their help that we can learn to understand those factors conducive to a correct response to stimulation, and the aberrations which the latter may become subject to.

It is well known that stimulation of the pacchionian corpuscles sets up a centrally travelling wave of depolarisation.[6] The amplitude of each transmitted impulse is a constant one; but, as Adrian has demonstrated so beautifully,[7] the frequency varies with the strength of the stimulus, and it is through modulation of the former, and variations in the area stimulated, that information as to object quality is imparted.

Up to now we have only a stimulus and a correct response to it, thus representing a univariable situation similar to that encountered in the nervous system of the cœlenterates, in whom neurotic or psychotic reactions are unheard of.[8] However, in 1956 Lowenstein demonstrated the presence of antidromic sympathetic fibres, which had the ability to modify incoming sensory messages.[9] Stimulation of these fibres both by electric current and by sympathomimetic agents resulted in an increased response to the applied sensory stimulus. When progressively stronger currents were utilised, the sensory fibres finally discharged without being actually stimulated, the result being a clear-cut case of sensory hallucination.

Inasmuch as touch occupies a relatively small place amidst the welter of stimuli that by their constant inrush disturb the serenity of the cerebral cortex, we will now turn to the auditory system, where a similar situation has been uncovered. Held, as early as 1893, demonstrated the presence of an efferent nerve leading from the area of the superior olive to the cochlea.[10] Being educated in the old Viennese tradition,[11] he lost these findings at the Operaball in 1894, and it was left for Cajal and Rasmussen to rediscover what is now known as the olivocochlear bundle. This tract modulates incoming auditory impulses. Galambo's experiments showing that the electrical potential of the cochlear nerve may be inhibited by stimulating these fibres,[12] again demonstrated the degree of cortical control imposed upon receptor organs.

These two tracts are only part of what may be termed the gamma efferent system. It is this system then, that is implicated in the normal or abnormal response to external stimuli, and which we must further examine in order to find those factors which determine normalcy.

DISPROPORTIONATE RESPONSES

Psychiatric literature abounds with cases which will suggest, when examined in this new light, that overactivity or underactivity of the gamma efferent system may precipitate neuroses or severer emotional disturbances.

An overactive gamma efferent system is the usual result of sensory deprivation. Studies such as those of Lilly,[13] and Meyer [14] show that hallucinations are frequently experienced after removal of external stimuli by either physical or pharmacological means. These sensory hallucinations are probably mediated by those very sympathetic fibres described by Lowenstein.[9] Mescaline probably acts in a similar fashion, and studies on its effects on the gamma efferent system are now in progress in our laboratories.[15]

Conversely, underactivity of the gamma efferent system may make the subject completely immune to external stimulation.[16] An interesting, perhaps congenital, example of such an underactive gamma efferent system has been

1. Selye, H., et al. Proceedings of the 13th Conference on Stress, Monte Carlo, 1958.
2. Steinbeck, J. Of Mice and Mazes. *Arch. Calif. psych. Ass.*, 1951, **14**, 211.
3. Adler, A. Freud as *I* Remember Him; p. 121. New York, 1922.
4. Bentham, J. Speech in support of the first Reform Bill. London, 1832.
5. Lao Tse. "A hasty man is a public misfortune." Translated from the Chinese in Hong Kong.
6. Gray, J. A. B., Sato, M. Properties of receptor potentials in Pacchionian corpuscles. *J. Physiol.*, 1953, **122**, 610.
7. Adrian, E. D. The Basis of Sensation. New York, 1928.
8. Coward, N. That Happy Breed; p. 165. Self Realisation Fellowship, Los Angeles, Calif., 1954.
9. Lowenstein, W. R. Sympathetic receptor facilitation. *J. Physiol.* 1956, **132**, 40.
10. Held, H., Die zentrale Gehörleitung. *Arch. Anat. Entwicklungsgesch.* 1893, p. 201. (A most interesting reference. The only copy extant is on the second floor of the medical library of the University of Würzburg. Ring bell and ask for Max.)
11. Strauss, J. Wine, Women, and Song.
12. Galambo, R. Suppression of auditory nerve activity by stimulation of efferent fibers to cochlea. *J. Neurophys.* 1956, **19**, 424.
13. Lilly, J. This is a marvellous paper. Someone told me about it at a cocktail party a few weeks ago, but I haven't been able to hunt up the reference in time for publication.
14. Meyer, J. S., Greifenstein, F., Devault, M. A new drug causing symptoms of sensory deprivation. *J. nerv. ment. Dis.* 1959, **29**, 54.
15. Huxley, A., Menkes, J. H., Critchley, M. The neurophysiology of mescaline. *Brain* (in the press).
16. "Blow, winds, and crack your cheeks! Rage! Blow! &c."—Shakespeare, W., *King Lear* III, 2.

ecorded by Mahler.[17] Her famous case, Lotta, showed arkedly diminished pain sensitivity to the point where ne day, out of pure malice, she scorched her lips on a lowing cigar-lighter.[18]

Thus it is the disproportionality between the input and he outflow of this gamma efferent system that is respon-ible for those deviations from normalcy noted in the pre-ent generation, and for acts performed which are at ariance with the stimulus inciting them (e.g., "beat-liks"). Why such an important neuronal system should ehave in as erratic a manner as it does, is not exactly lear at this time. One possibility is that some of the vital elay systems along its paths have become invaded with what we have termed nonconforming neurons, such as previously described for the optic system.[19]

Should we accept such a hypothesis, we then acknow-edge that the schizophrenic reactions are not directly due o defects on a molecular or enzymatic level, but are the esult of disruption on a higher (i.e., on a neuronal) rganisational plane.

Such a theory is very disturbing, especially in the light of the innumerable papers (discretion will not allow me to ite references at this point), which are concerned with determinations of cæruloplasmin, neuraminic acid, tryptophan metabolism, protein centrifugation patterns, &c., &c., all of which are found to be abnormal in schizophrenia, statistically speaking that is.

Yet, going back to primary causes, even the organisation of the central nervous system is genetically controlled, and therefore depends on enzymatically directed reactions occurring mainly, or perhaps even exclusively, during the developmental phases. A critical reaction might not be able to proceed during this period, resulting in an organisational defect of the gamma efferent system. Such a defect, which has as its main abnormality a disproportionate response between input and output, would be in many ways similar to, but infinitely more subtle than, the organisational defects seen in microgyria for instance.

FORTHCOMING WORK

In conclusion, we must apologise to the reader, to the editor, and perhaps even to the printer, for having gone so far astray. Starting with a neuron, we have jumped in and out of afferent and efferent tracts, with results which unencumbered by data, recall Pirandello's *Cosi e, se vi pare* (It is so, if you think so). A fuller discussion of this concept and its application to scientific data and their interpretation will be forthcoming (Pirandello and Scientific Research).

17. Mahler, M. S. Child Psychosis and Schizophrenia. *Psychoanal. Study Child.* 1952, **7**, 286.
18. Ronson 'Prince Charming' $17.85 F.O.B. New York.
19. Menkes, J. H. Progressive non-conformism in the lateral geniculate nucleus of man. *Lancet*, 1958, ii, 1368.

THE GEKOCHTEUNDGEBROCHENEEIERSCHALE PHENOMENON

Mechanical and Physiological Factors

BRIAN MAEGRAITH

DENATURATION by heat of the protein content of the encapsulated ovum (or egg) of *Gallus domesticus* has been frequently demonstrated; but a difficulty encountered in all experiments has been the frequent appearance of the Gekochteundgebrocheneeierschale phenomenon.

Makewater (1959) has now advanced evidence that in the normal encapsulated ovum a compartment of gas is imprisoned immediately beneath the outer calcareous envelope. The well-known law of thermodynamics which states that gas will expand when heated and if confined will exert proportionate stress pressures on the confining medium has been found to apply to the ovum when it is exposed to heat, especially in the region of 100°C. The lines of force exerted and their stress patterns in the continuum of the solid envelope are such that inverted implosion may become manifest.

Disintegration of the calcareous envelope and consequent escape of the protein matrix during the process of *überwallen*, as Wirtschafterin (1958) designates it, are the two cardinal features of the whole Gekochteundgebrocheneeierschale phenomenon. Makewater's contribution to its control is based on the hypothesis that the phenomenon could be inhibited by the creation of artificial escape paths or canals for the enclosed gas, thus obviating hyperdynamic overloading at the pressure surfaces. This was accomplished by drilling a critical aperture in the interface between the envelope, the internal ovum, and the liquid environment. Trial experiments showed that an artificial communication between the gas-containing compartment in the region of the rounded terminant of the egg-mass acted as a true Gekochteundgebrocheneeierschale inhibitor. This of course was achieved by thermodynamic-gas/liquid equilibrium which prevented autoclysis.

Our own experiments confirm Makewater's observations.

EXPERIMENTAL

6 recently delivered enveloped ova were divided into three experimental groups of 2 each. On three successive days one group was immersed in cold water and raised to 100°C for two minutes. Of the 6 samples, 5 developed extensive envelope stress patterns involving the escape of protein into the liquid environment. One sample became "poached" (Perkins 1956).

Over a further period of three days three batches each of 2 enveloped ova were heated in the same manner. In each case, before heating, a Makewater canalisation was performed in the rounded terminant. The results were remarkable: stress signs were absent and denaturation was absolute.

To determine the relative gas/liquid interchange characteristics, a control group of enveloped ova (or eggs) were canalised as above, heated to 100°C for two minutes, and then plunged into cold water containing blue dye (Parker and Stevens 1910). The intradural cavities of each egg accepted some of the pigmented fluid, thus proving Charles's law.

Controls, canalised in the pointed (as distinct from the rounded) terminant, were consistently deprived of protein to a degree which led to the condition described by Edelweiss as *hervorgebrochen.*

DISCUSSION

With a view to controlling the amount of gas and its distribution within the envelope of the ovum, ortho-oval procedures have been suggested:

Addelhauer (1959) has raised donors on a diet of bicarbonate of soda and acetic acid, and claims that by certain postural arrangements he can distribute the gas wherever he so desires within the envelope or shell. In this way he has been able to distribute the gas equally at either end of the egg. In these circumstances, of course, a Makewater canalisation at either end would serve its purpose during the process of denaturation.

Again, certain authorities have proposed that the gas compartment might be redistributed within the envelope by manipulative inversion within the cloaca at the time of, or shortly preceding, delivery. Standard obstetric techniques, including the use of forceps, have been proposed for this manipulation.

Such problems have not escaped the notice of geneticists. For instance, Eierkopf (1958) and Kuru (1957) have pointed out that there are strong indications of the possibility of the appearance of allelomorphic mutants which are determined by mendelian dominant transmission associated with incomplete sex-determined genes which are themselves dependent on relevant chromosomic deficiencies.

The importance of this cannot be underestimated. Thus, it is clearly possible that allelomorphic mutants may arise which determine the delivery of an egg which is equally rounded (or equally pointed) at both ends. If such a mutant were produced it would inevitably be necessary to combine with it an equal distribution of the relevant gas bubble, since if the gas were confined at one end only it would lead to inconsistency in delivery pattern. Moreover, if each end were equally rounded and was, moreover, equidistant from the other end, it would be impossible to apply successfully the Makewater technique of canalisation in more than the appropriate mathematical chance ratio ($p = <$). In such circumstances incubation at adequate temperature, even though it led to denaturation, would not be without risk of the generation of the Gekochteundgebrocheneeierschale phenomenon.

On the whole, we recommend that geneticists should refrain from breeding allelomorphic mutants unless they are prepared to develop parallel allelomorphs in donors and operators alike.

SUMMARY

If you prick the thick end of a hen's egg, it won't burst when you boil it. *Das ist zum brechen.*

Public Health

Rehousing the Disabled

IN his report for 1959 [1] Dr. J. A. Scott, medical officer of health to London County Council, stresses the difficulty of selecting families for rehousing on medical grounds. In 1939 1000 applications backed by medical certificates were received, and, in 1945, 450. But in 1950 they numbered 44,000. An analysis of 1000 certificates in 1947 showed 20% to be genuinely urgent, and 40% less urgent; the remainder contained no grounds for action. In 1948 a similar analysis gave percentages of 10, 35, and 55 respectively.

Clearly general practitioners were under pressure to produce certificates; and from 1957 onwards the Council asked doctors to send a letter instead, describing any serious medical condition which rehousing might benefit. Between 40 and 50 letters a week are now received; practitioners agree that the new system is an improvement.

Between 1945 and 1955 the Council rehoused 75,000 families; owing to the growing lack of building sites slum clearance must have priority; but some accommodation is still set aside for medical cases.

When a doctor's letter is received, a health visitor is sent to obtain further details, and, whenever necessary, a public-health inspector also reports on the premises. The medical officer at divisional level decides whether the application is justified; and the decision to nominate for accommodation is made by the county medical officer of health or his deputy. Nominations are then submitted to the housing committee, which considers all the information thus made available.

In three years, 521 cases have been recommended for rehousing because of pulmonary tuberculosis, and 1122 for other medical conditions. In more than half the cases application is made for accommodation on the ground-floor. This is not always possible; often only first-floor accommodation is available. Of the first 600 non-tuberculous cases nominated, 174 had locomotor disorders and wished to avoid stairs: of these, 30 living on upper floors had had amputations, 41 were arthritic, 40 had lower-limb pareses (poliomyelitic sequelæ), and 31 had disseminated sclerosis. Cardiac conditions numbered 164. Often the exertion involved in climbing stairs to a third- or fourth-floor flat within easy reach of the place of work must be weighed against a long and tiring journey to a distant ground-floor flat. Priority in cardiac cases is given to those still working and to young mothers bringing up a family. Many patients rehoused may not benefit greatly themselves, but the overall improvement in their family's living conditions may be considerable. Some refuse offers of rehousing. Higher rent is one reason, disappointment at not being offered new premises another. Localities must be chosen where the families' personal contacts will not be severed.

Dr. Scott concludes that it is difficult to lay down any rational set of rules for guidance: rehousing is less of a scientific process than an exercise in the practice of the art of medicine.

1. Report of the County Medical Officer of Health and Principal School Medical Officer for 1959. London County Council. Obtainable from the Information Bureau, County Hall, S.E.1. Pp. 166. 4*s*.

Mental-hospital Admissions by Area

The General Register Office has classified according to the administrative areas in which the patients lived the 88,943 admissions to mental hospitals in England and Wales in 1957.[1] The cases are also classified according to sex, 5-year age-groups, and diagnostic category and into first or subsequent admissions. Admission-rates can be deduced from the Registrar General's population estimates for 1957.

While 3 Cardiff residents of every 1000 went into a mental hospital (the highest rate), only 1·2 per 1000 did so in Manchester. Wider use of domiciliary, day-hospital, and general-hospital facilities must have contributed to this very low Manchester figure. High rates did not characterise industrial areas—in fact, in Cornwall and Norfolk (2·5 and 2·1) the rates were substantially higher than in Staffordshire and Durham (1·7 and 1·6)—but in general the rates were higher in town than in country. The highest figures for London boroughs came from Stoke Newington (2·9) and Stepney and Chelsea (both 2·8).

The diagnostic categories are: schizophrenia; manic-depressive reaction; senile and presenile psychoses; other psychoses; psychoneuroses; character, behaviour, and intelligence disorders; and other. Manic-depressive illness (32·7% of admissions) outnumbered any of the other six categories, with the usual preponderance of women and a peak age of 45. In schizophrenics (20·2% of admissions) the peak age of admissions was ten years earlier, and the sex-distribution was about equal. In London the proportion of schizophrenics was higher (28%), but the proportion was greatest in Manchester (36%); rural proportions were lower—e.g., in Cornwall (11%) and Hertfordshire (9%).

Unfortunately mental subnormality is grouped with disorders of personality and behaviour; and the figures on which the report is based are but a function of the administrative and diagnostic practices in each area, so that regional differences must be interpreted with caution. Thus the report is primarily of administrative interest. The incidence of mental illness in the population is a subject in which we lag behind other countries. Data showing the changes from year to year would be useful, as would correlation with other variables—for example, bed numbers, average length of stay, day-hospital services, non-statutory beds in general hospitals, and consultant sessions. Nevertheless, this report provides valuable pointers to fields in which closer study might be most rewarding.

1. Areas of Residence of Mental Hospital Patients. *Stud. med. Popul. Subj.* no. 16. H.M. Stationery Office, 1960. Pp. 177. 15*s*. 6*d*.

In England Now

A Running Commentary by Peripatetic Correspondents

MOST of the other girls leaving school that year hoped to be nurses or secretaries, but I wanted to be a circus rider. There was nothing else for me to do. Not in the way of a career. So when my headmistress persuaded me that it was impossible, I shrugged my shoulders and said, "Oh well. I'll have to get married and have six children."

I took my children to the circus for their Christmas treat. It was their choice but I was pleased. They all laughed when a dwarf squirted water from the top of his head. The boys liked the tigers and the clowns. But when a big white horse sauntered round the ring and a girl in sequins turned somersaults on his back, I glanced at my daughter, Emmeline. There was a look in her eyes that I had never seen before.

The dwarf who squirted water from his head jumped up and down in front of us and said, mysteriously, "Your turn will come." While two shining acrobats writhed in a crescent moon high above our heads I saw, in the darkness below, five men, a tall pole, a long rope, and a pulley. When the lights went up the ringmaster said, "Now we want a member of the audience to do some bareback riding." At my side, Emmeline gasped, half rose to her feet. "Anyone over the age of eighteen." "Oh," moaned Emmeline. "I'm only six. Even the boys aren't eighteen." "Will any gentleman in the audience come forward? And it doesn't have to be a gentleman. Perhaps a lady would like to try? Come along. Come along." "Go on, Mummy," whispered my eldest. "It's the chance of a lifetime."

I stood in the ring. Too late I remembered my straight, tight skirt, but I comforted myself with the knowledge that my legs were still presentable. They tied a broad leather belt around my middle and hooked me to a rope. Across the pulley a man held the other end. The big white horse cantered in. The gates closed. "Now," said the ringmaster. "Run and jump. We won't let you fall."

I ran and jumped and missed. Not a hope. Screams of laughter. Wolf whistles. "Try again." I tried. This time as I jumped I floated through the air and managed to grab the two handles on the horse's back. I was up astride. My skirt slid upwards. Nylons, suspenders, more wolf whistles. But I didn't care. Round and round we went. I knew this was the life for me. "Now on your knees!" Easy. I held on tight and twisted. I was kneeling, quite secure on that broad white back. I could even see the faces in the half-light as we circled. I grinned at my children. Emmeline's mouth hung open. "Now on your feet!" This wasn't so good. But the friendly tug of the rope as it tightened across the pulley gave me confidence. In a moment I would be there, standing up, perhaps even dancing. Just a question of balance. Now. Up. Do it slowly. Take care. Up. Now, let go.

I swayed and moved my leg outwards to keep my balance. But I forgot my skirt. The rope jerked as I grabbed at the handles. The world turned over and I swung through the air. Far away I could see the horse still cantering round the ring. I swung back across his head, and below I could see the faces of my children, the boys laughing, Emmeline worried. Then I swung away again, dangling helplessly in the air. The mother of six who wanted to be a circus rider.

The boys are still very proud of their mother, which is comforting. But Emmeline hopes to be a nurse when she grows up.

* * *

Yesterday I came across a little-known side-effect of systemic penicillin therapy. A patient with an infection of the upper respiratory tract was advised to have penicillin by injection. He agreed, but asked, "Can I have it in my right arm, doctor?" "Certainly; are you left-handed?" "No. But when I have it in my left arm my watch stops."

* * *

Let's make it a National Health Service Christmas—join our Christmas Club and shop at the surgery! Ask your Doctor NOW for your FREE copy of the Ministry of Health's fabulous 800-page illustrated catalogue of Special Shilling Gift Parcels! YOU choose them, WE send them! May we suggest:

The Home Surgeon Kit.—Create your own emergencies for Ward 10! Contents include set of tools and complete instructions—e.g., "Your gallbladder and how to remove it."

The Hypochondriac's Hamper.—Contents include 250 tranquillising capsules (with the exciting new centres): and choice of twelve disconcerting Aperients. Also Stomach-pump, A.C. or D.C. (with little robins on the lid, postage and packing extra). One copy of H.M.S.O. publication *How to tell How You Are.*

The Gay Deceiver Gift Parcel.—Contents include: Wig (choice of six smashing styles, including the chrysanthemum, etc.), one pair rose-coloured spectacles, one set dentures, deaf-aid, and choice of artificial limb and/or kidney, glass-eye, elastic hosiery or corsets. One copy of H.M.S.O. publication *What Are Little Girls Made Of?*

The Soho Special.—Packed in handy cosh-sized Christmas stocking. Contents include razor with spare blades, brass knucks, nine inches of bicycle-chain, and a packet of assorted wound-dressings. Also vouchers for FREE ambulance get-you-home service, six novel suggestions for alibis, and a psychiatrist's certificate guaranteeing the bearer is not responsible for anything.

Customers will thrill, too, at the Ministry's sticky Yule-tide labels, bearing seasonable greetings, such as "One tablespoonful three times a day in water" and "Stow away from Boilers".

General Practitioners of course can hardly wait for details of the Ministry's competition for Ye Beste Decorated Quainte Olde Englysshe (Britissh) Waiting-Roome, with contemporary periodicals.

There will be inspections of all Festive Premises to detect any reactionary deviationists and to ensure that over Christmas such premises are kept open day and night, with the General Practitioner greeting the customers by emerging from the waiting-room fire-place disguised as Father Christmas.

* * *

During last week's rainy weather it was reported that the angels in Regent Street had all mysteriously developed abdominal distension and swung in apparent celestial pregnancy above the milling shoppers. Mr. Beverley Pick, their designer, was greatly disturbed by their changed appearance, and treatment was instituted by attaching a sharp spike to the end of a long pole which was then thrust into each angelic abdomen. But does not this treatment by remote-control paracentesis suggest that the true diagnosis should really be Pick's disease?

* * *

I am a great believer in toothpicks. Since I began using them three or four years ago I have had no caries whatever. I suppose dentists do not advocate them more freely because of the risk of their being used ill-manneredly. Perhaps the toothpick is in a position opposite to that of war, which Oscar Wilde said would have its fascination as long as it was regarded as wicked: when it was looked upon as vulgar, it would cease to be popular. Let us, then, have a campaign to emphasise the toothpick's exciting association with wickedness: let each Sir Jasper in every melodrama be a flagrant user of these dastardly instruments.

* * *

My first Christmas card of this season came from a friend in New York. My appreciation of this Yuletide greetings was only a little marred by the bold postmark on the envelope—Report Obscene Mail to your Postmaster.

* * *

CAROLS FOR PSYCHIATRISTS

I

Hurrah for crime and sex anomalies,
Perversions all and problem families,
Without which at this festival
We would not have the wherewithal.

II

To comfort always is our task I hear,
But tranquillisers now give way to beer
And from neurotics sad or frisky
Thankfully I turn to whisky.

Letters to the Editor

THE CASE AGAINST TRENDELENBURG'S POSITION

SIR,—I have been waiting for others to scramble into the arena and pick up the glove trailingly thrown, not only by your annotation, but also by Dr. Inglis in your issue of Dec. 10, and previously by Dr. Inglis and Mr. B. N. Brooke.[1]

From Celsus (40 B.C.) and Abulcasis of the 11th century, down to Percivall Pott of the 18th, and modern times, the semi-inverted position has been used for the treatment of abdominal injuries and replacement of intestine, for the simple reason that the ancients instinctively recognised that this position induced a negative pressure in the abdomen. It was, however, Friedrich Trendelenburg (1884–1924) who first observed that " when the peritoneal cavity is opened with a patient at an angle of 30–40 degrees, a negative pressure sucks air into the cavity with an audible sound, and as a result the intestines bunch together in the epigastrium, so causing no concern to the surgeon ", and he goes on to state that " every step of a pelvic operation can then be done under direct vision ", a thing which is absolutely true.

In a long career and experience of many countries, I have yet to see the postoperative shock or cardiovascular and pulmonary disasters experienced in Birmingham from the use of the Trendelenburg position in these days of skilled anæsthesia and relaxants. Certain it is that a moderate inverted position is essential for a Wertheim or any high-class difficult surgery of the tubes. Moreover, as was shown by Spalding in his classic paper [2] which was backed by Sir Heneage Ogilvie, when such patients are put back to bed in a prone position rather than Fowler's, drainage, and particularly lymphatic drainage, is better and recovery more speedy, with less risk or incidence of thrombosis and embolism.

If there be any banishing, by all means let the gynæcologist give up the cosmetic bikini-wishing Pfannenstiel (1862–1909) incision. This indeed is a real relic of the bad old days of anæsthesia, possessing multiple disadvantages, the greatest being that removal of the large tumour and/or complicated pelvic surgery is made a nightmare of inefficiency. Indeed, unless both recti are really cut across it is impossible to see or do properly any delicate or complicated work with that celerity and bloodlessness that modern technique demands.

London, W.1. V. B. GREEN-ARMYTAGE.

SIR,—Apart from the six objections—respiratory and cardiovascular complications, calf-vein thrombosis, nerve injuries, late shock, and an irritated anæsthetist—mentioned by Swain,[3] there is another possibility referred to by Abel and Lewis.[4] They described local baldness in eight women who had had long gynæcological operations, mostly with Trendelenburg tilt. The baldness was fortunately reversible. The histological changes seen in the skin could be reproduced experimentally in cats by circumscribed pressure on the head.

Amsterdam. T. WILHELMUS.

1. Inglis, J. M., Brooke, B. N. *Brit. med. J.* 1956, ii, 343.
2. Spalding, J. E. *Lancet*, 1946, i, 643.
3. Swain, J. *Med. J. Aust.* 1960, ii, 536.
4. Abel, R. R., Lewis, G. W. *Arch. Derm. Syph.* 1960, **81**, 34.

CHEMOPROPHYLAXIS IN CHRONIC BRONCHITIS

SIR,—I would be grateful for a chance to comment on your leading article of Dec. 10.

Of course the chronic bronchitics described in the Swiss trial improved: they had been removed from their usual environment and were getting rested in hospital. The drugs they received were of minor import.

But what of the chronic bronchitic in his normal (" normal " in the sense of " usual ") habitat?

There he sits, poor fellow, in his damp house, with factory and power-station chimneys all around. He's been at work all day, queuing in the rain afterwards for an overcrowded bus. On the mantelpiece, within easy reach, is a jar full of ' Omnimycin '; and he has been told to keep on eating them for the next few months.

It's all like Grandma's Daily Purge to keep her Bowels Moving.

London, S.W.11. R. WINSTON.

HOSPITAL SHOPS

SIR,—I am impressed by the argument in your correspondence columns of Dec. 3 and 10 concerning the illogicality of the sale of cigarettes in hospital shops.

I have discussed the matter with a number of my colleagues who are all, I find, in general agreement with the principle involved.

There are, however, a number of modifications in the views expressed dependent on the special interests of the doctors concerned. The ophthalmologist feels that cheap books with small print are undesirable: the psychiatrist is doubtful about the large print in the newspapers: the rheumatologist, pædiatrician and diabetic physician agree in condemning the sale of sweets and chocolates. The casualty surgeon, noting the increased incidence in domestic burns, would prefer that matches be not sold. It was a misanthrope who suggested " Get well " cards were also illogical.

PRO BONO PUBLICO?

RADIOLOGICAL HAZARDS TO PATIENTS

SIR,—I should like to go further than Dr. Gibson (Dec. 3), who re-emphasises the dangers and inadequacies of fluoroscopy in the detection of early pulmonary tuberculosis, and suggest a complete reappraisal of the value and limitations of fluoroscopy generally in diseases of the chest.

Apart from its rare use in detecting abnormal movement of the diaphragm and irregular cardiac behaviour, it is doubtful whether fluoroscopy should ever be used as a *preliminary* measure.

The safer procedure is to obtain a postero-anterior radiograph first, supplemented by further projections and possibly fluoroscopy as indicated by the initial radiograph. Intrinsic disease of the œsophagus, of course, is an indication for fluoroscopy.

It should be realised that the use of image intensifiers, whilst giving a greater illumination of the field and reducing the dose to the patient as compared with conventional fluoroscopy, still leaves unsatisfied the requirements of a permanent record and a rough idea of the radiation dose received by the patient.

Sheffield. THOMAS LODGE.

SIR,—Your leader of Dec. 10 implied that the manufacture of diagnostic machines as alternatives to radiological equipment (i.e., foreign-body locators) is now contemplated in this country.

Your readers will doubtless be interested to learn that this matter has engaged our attention and research for the past two and a half years, and that a foreign-body locator is now in production. While one of the initial production batch was in use at a leading Midlands hospital, recommendation was made for us to attend the physics department of a London hospital particularly interested in this subject, with a view to adapting our machine for work other than the purely ophthalmological uses for which it has been primarily designed.

Accordingly the machine equipped with only the standard ophthalmological probes was tested for location of a needle fragment in a patient's back. The test was immediately and outstandingly successful, as a result of which further specifically designed probes are being prototyped for location work on parts of the human body other than the eyes.

This company will be happy to reply to all inquiries concerning the detailed specification of this foreign-body locator.

F. N. HAM
General Manager,
Keeler Optical Products, Ltd.

London, W.1.

COST OF THE HOSPITAL SERVICE

SIR,—A daily newspaper has drawn the attention of its readers to the alarming rise in the cost of the Hospital Service. I suggest that the fault lies partly in the Government's attitude to general practioners in this country.

The cost of the Hospital Service together with the long period of waiting for outpatient appointments could be reduced in two ways:

Firstly, pathological and X-ray facilities should be available to all practitioners.

Secondly, some form of grant and inducement payment should be made to general practitioners who wish to do their own minor surgery. This would allow the consultants more time to devote to the more important cases while allowing the young practitioner to exercise the skill he acquired when doing his numerous house-jobs, which is at the present moment entirely wasted.

Newport,
Isle of Wight.

J. A. C. TERRY.

POSTPARTUM PRE-ECLAMPSIA

SIR,—Dr. Salzmann (Dec. 3) is largely though not essentially in agreement with my hypothesis.

He agrees that (*a*) corticosteroid increase is not of primary significance in pre-eclampsia; (*b*) the contracting uterus post partum and intrapartum provokes renal ischæmia; and (*c*) ergometrine heightens uterine activity.

He differs from me in believing that the products of decomposition of the red infarct provoke renal ischæmia, whereas I have shown that the resistance to stretch of the myometrium is responsible for this renal change in pregnancy and post partum, both experimentally and from clinical data. Franklin and I have further shown that renal ischæmia can be produced by nephrotoxins even to the extent of a complete renal shutdown, and Dr. Salzmann's view based on Professor Young's observation cannot be entirely denied.

But we do know that red infarcts are present without pre-eclampsia accompanying them, while the toxæmic state can exist in their entire absence; and there is no correlation between their extent and the degree of toxæmia. Neither can they be used to explain the difference in incidence of pre-eclampsia in primiparæ and multiparæ.

Dr. Salzmann raises the point that even in the premature and very small baby toxæmia can supervene and thereby appear to upset the uterorenal thesis. This apparent contradiction can be explained by the following facts. The kidney of chronic hypertension (in which evidence is accruing of renal ischæmic changes [1]) would reasonably be expected to be more responsive to the uterorenal reflex; the vascular effect on myometrium showing chronic hypertensive changes would be earlier and more marked and fœtal growth thereby impeded. This is supported by the brilliant research of Mr. G. W. Theobald, who, in interrupting the uterorenal reflex pathway by denervation of its tract, succeeded both in increasing the fœtal size (and securing viability) and in preventing toxæmia, hitherto an accompaniment of these pregnancies.

Worthing.

J. SOPHIAN.

BLOOD-CHOLESTEROL AND ASPIRIN

SIR,—In a preliminary communication (Nov. 19) Dr. Eidlitz reported that aspirin (1·5 g. daily) reduced the blood-cholesterol level in 10 patients with cardiovascular disease. In a group of 21 hypercholesterolæmic patients, to whom aspirin was administered for eight weeks, we [2] found that doses of less than 4 g. daily usually failed to lower serum-cholesterol. More than 5 g. of aspirin daily produced a significant and consistent fall in serum-cholesterol but no change in the cholesterol-phospholipid ratio or the beta-lipoprotein cholesterol. These observations also indicated that during aspirin therapy the serum-cholesterol levels are inversely related to the level of serum salicylate. With a dose of 5 g. aspirin daily, the incidence of side-effects was so high that we did not think that aspirin was a practicable treatment for the reduction of hypercholesterolæmia. A satisfactory explanation of these contrasting findings is not immediately obvious.

W. D. ALEXANDER
A. I. MACDOUGALL.

Glasgow.

M. F. OLIVER
G. S. BOYD.

Edinburgh.

MENTAL OBSERVATION WARDS

SIR,—Although I am more concerned myself with the psychological conclusions to be drawn from mental observation-ward practice, I think Dr. Gooddy and his colleagues (Dec. 10) may be interested in a clinical table of patients seen in the unit at St. Francis Hospital, East Dulwich, during part of the years 1949–50.[3]

Stone House,
near Dartford,
Kent.

J. P. CRAWFORD.

"THEY NEVER TELL YOU ANYTHING . . ."

SIR,—I agree with Dr. Loudon (Dec. 3) that the "of course they never tell you anything" of those patients that leave hospital is seldom true in its literal sense—but not always. Everybody knows that many patients leave hospital with little knowledge of what is wrong with them, because somebody has forgotten or failed to explain to them their diseases in plain language.

Everybody talks as well of how overcrowded the outpatient department is, but this is no excuse for the many who say they cannot waste time explaining "everything" to the patient.

All every patient wants to know is the answer to the questions: (1) what is wrong with me? (2) how bad is it? (3) how long will it last? (4) what treatment are you going to give me? (5) shall I be "all right" afterwards? By making a rule to answer all these 5 questions for every patient before he asks them, very little time is spent and very many worries and troubles are spared to the anxious patient.

1. Cook, W. F. Renal Association meeting, Oct. 27, 1960.
2. Alexander, W. D., Macdougall, A. I., Oliver, M. F., Boyd, G. S. *Clin. Sci.* 1959, **18**, 195.
3. *Practitioner*, 1954, **173**, 696

This applies particularly to the surgical patient. It must be realised that an operation, however trivial, is the utmost event in the lives of most patients; so no wonder they are so concerned, wanting to know the smallest details that may seem ridiculous to us but are an enigma to them.

Winford Orthopædic Hospital, near Bristol. J. S. BAENA.

TREATMENT OF OBESITY BY THE HIGH-FAT DIET

SIR,—I read with considerable interest Professor Yudkin's and Miss Carey's article (Oct. 29) as well as Professor Yudkin's letter of Dec. 10.

I have for the past two years been following a diet such as they describe. It is effective in controlling a tendency to overweight, and the difficulties pointed out by Dr. Sasieni (Nov. 12) are not insurmountable. Other problems arise, however, in the long run: a certain amount of hunger is inevitable (and yet more protein is no answer since this increases the calorie intake and thus weight) and over many months this nagging hunger leads to irritability and nervousness. Moreover, even after eating habits have been changed, total adjustment to this diet is hard to achieve; it does demand an unceasing self-discipline, and this too imposes a cumulative burden of strain.

I wonder whether many of Professor Yudkin's patients have happily followed this diet over a number of years without suffering any such stress in the long run?

Queen's University, Belfast. LILIAN R. FURST.

ASSESSMENT OF CEREBRAL BLOOD-FLOW WITH RADIOACTIVE TRACER

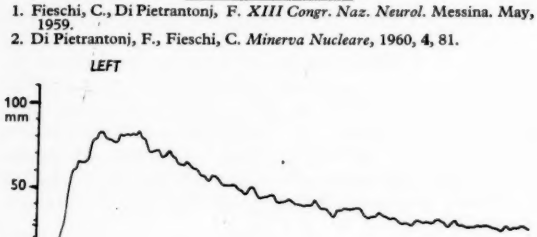
SIR,—We have been studying [1 2] the cerebral circulation by a method similar to the now widely used technique of following an injected tracer during its transit through the heart with an external scintillation counter.

To study the cerebral blood-flow (C.B.F.), 30–50 μC of ^{131}I-serum-albumin are given by rapid intracarotid injection, and the passage of the tracer through the cerebral vessels is recorded by a directional scintillator. The counter is placed on the head, on the same side as the injection, and is connected to a ratemeter and a writing recorder.

The tracings (radioencephalograms, R.E.G.) show a sharp rise, followed by a short plateau, and a dropping phase (see figure). By plotting the tracings on semilogarithmic paper, the last part of the curve becomes linear, following an exponential law, and can be expressed by its half-time ($T_{0\cdot5}$). $\frac{0\cdot693}{T_{0\cdot5}} = R$, the fractional turnover-rate of the cerebral blood-volume. In normal cases $R = 0\cdot24 \pm 0\cdot037$.

$R = \frac{\text{C.B.F.}}{\text{cerebral blood pool}}$ and increases after the inhalation of 5% CO_2 in O_2, in accord with the increase in C.B.F., demonstrated by the nitrous-oxide technique.

1. Fieschi, C., Di Pietrantonj, F. *XIII Congr. Naz. Neurol.* Messina. May, 1959.
2. Di Pietrantonj, F., Fieschi, C. *Minerva Nucleare*, 1960, **4**, 81.



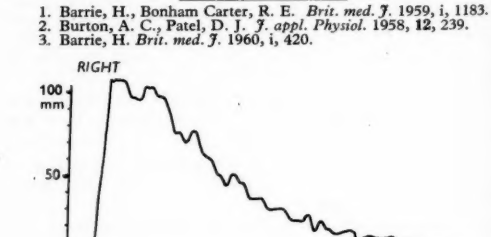


Fig. 1—Passage of tracer through cerebral vessels as recorded by directional scintillator: left, thrombosis; right, normal.

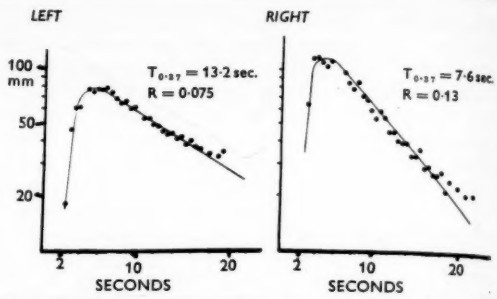


Fig. 2—Plotting on semilogarithmic paper: left, thrombosis; right, normal.

Significant differences in the R.E.G.s on one side and the other are observed in patients with thrombosis of one interal carotid (see figure).

We have found this method easy and innocuous, and we think it well suited for revealing gross alterations in cerebral blood-flow.

University of Genoa. C. FIESCHI
F. DI PIETRANTONJ.

PROTEIN IN HYALINE MEMBRANE

SIR,—In your excellent summary (Nov. 5) of new concepts in hyaline-membrane disease the statement that "no effective remedy is in sight" is perhaps unduly pessimistic.

The syndrome is characterised by progressive sternal and intercostal retraction, and that this is a clinical manifestation of abnormally high intrathoracic negative-pressure swings is now common knowledge. Exerted some forty to fifty times a minute, these alone are theoretically capable of damaging the pulmonary capillaries of a premature infant.[1] Moreover, a high negative pressure increases the pressure gradient between pulmonary capillaries and alveoli,[2] and this may well constitute the driving force of the exudate from which the hyaline membrane is ultimately derived.[3] If this reasoning is correct, then positive-pressure lung inflation, by diminishing capillary trauma and by reversing the pressure gradient between capillaries and alveoli, should be the logical treatment.

Attempts to put these views into practice in the past two years have admittedly been disappointing. The infants so treated, however, were small bad-risk premature babies weighing only $1^1/_2$–3 lb., and were in the terminal stages of the disease. Continuing sternal retraction suggested that high enough pressures were not being used, and, in the absence of a mechanical ventilator, efforts were probably not persistent enough. It is perhaps insufficiently realised that our knowledge of the pressures used in lung inflation stems largely from work done on

1. Barrie, H., Bonham Carter, R. E. *Brit. med. J.* 1959, i, 1183.
2. Burton, A. C., Patel, D. J. *J. appl. Physiol.* 1958, **12**, 239.
3. Barrie, H. *Brit. med. J.* 1960, i, 420.

excised lungs with airtight cannulæ. In practice, higher pressures are necessary and this work requires urgent reinvestigation with the free-lying endotracheal tubes at present in common use. Also, for positive-pressure respiration to be effective in hyaline-membrane disease, it would need to be used, from theoretical considerations, from the onset of the disease. Our faith in the value of positive-pressure respiration has been strengthened by our recent experience with a $2^1/_2$-lb. premature infant with severe hyaline-membrane disease who was successfully ventilated for 60 hours, when death occurred as a result of cerebral hæmorrhage. There have also been two reports of this method of treatment with survival. First, Benson's group,[4] using tracheostomies and curare, and now Colgan and coworkers,[5] using endotracheal intubation, have successfully treated four infants with respiratory distress by prolonged mechanical positive-pressure ventilation. Whilst none of the four infants had a birth-weight of under 5 lb., the results are sufficiently encouraging to merit a trial of this treatment for hyaline-membrane disease.

St. Thomas's Hospital, London, S.E.1. HERBERT BARRIE
R. P. WISE.

CANCER OF THE ŒSOPHAGUS

SIR,—We should like to thank Mr. Dark (Dec. 3) for his interesting and constructive suggestions, but we do not share his enthusiasm for the Mousseau-Barbin œsophageal tube. We do not feel it fulfils all our requirements. The largest Mousseau-Barbin tube has an external diameter of 16 mm. and the lumen is barely large enough to allow the patients to swallow semi-solids. The largest tube we use has an external diameter of 1 inch (25 mm.) and enables the patient to eat a normal diet provided that fluids are taken frequently during the meal.

The main point of our argument is that a malignant stricture of the œsophagus can be dilated very much further than one might think would be possible without the wall splitting; this fact is not widely appreciated. The chief disadvantages of the Mousseau-Barbin tube are that its lumen is too small and it is expensive.

Finally, we should like to stress once again our belief that it is safer to dilate the stricture by pulling something through from below than attempt dilatation through an œsophagoscope.

Royal Marsden Hospital, London, S.W.3. W. P. GREENING
GORDON S. RAMSAY.

PNEUMOCONIOSIS

SIR,—Working among a mining community, I am concerned how often some men are told, by consultant physicians, chest physicians, and their own doctors, that they have pneumoconiosis, when there is little radiological evidence for this diagnosis. Very often this opinion is expressed without a true knowledge of the radiological appearances of category-2 (certifiable) pneumoconiosis.

When such an opinion is given it is not often realised that the aftermath can be that the patients are rejected by the pneumoconiosis panel. At best, the patient feels doctors do not know their own minds. At worst, it leads to the development of symptoms where none existed; to unnecessary changing of jobs and economic difficulties; and to a permanent grudge in a man who feels he is being denied compensation.

Most miners who have worked a lifetime in the pits come to expect a certain amount of "dust on their lungs". If radiological evidence confirms this, then the man should be told in these terms, qualified by advice to apply to the pneumoconiosis panel, who will be the final arbiters and decide whether the amount of dust justifies certification. The man will then feel that he has had good advice but, at the same time perhaps, be relieved to learn that the dust on his lungs is not sufficient to be classified as pneumoconiosis.

Worksop, Notts. A. F. OAKLEY.

SIMULTANEOUS THROMBOTIC THROMBOCYTOPENIC PURPURA AND AGAMMAGLOBULINÆMIA

SIR,—Many authors have classified thrombotic thrombocytopenic purpura (T.T.P.) as a so-called collagen disease and accepted an immunological pathogenesis based on an antigen-antibody reaction. The recent observation of T.T.P. in two children with agammaglobulinæmia and an adult [1] with a partial antibody-deficiency syndrome is against this hypothesis.

CASE 1.—A boy of 16 months with congenital agammaglobulinæmia and constant lymphopenia developed an acute febrile illness within 24 hours of a combined vaccination with triple antigen and T.A.B. The hæmoglobin fell from 16 to 4·8 g. per 100 ml. in 3 days (reticulocytes 19·2%, platelets 84,000, bilirubin 1·4 mg. per 100 ml., direct Coombs test negative). No abnormal antibodies could be detected in the indirect Coombs test in saline and in albumin at various temperatures. The child died 14 days after the vaccination. Necropsy revealed typical subendothelial and intravascular fibrinoid deposits in the capillaries and arterioles of virtually all organs.

CASE 2.—A girl of 6 months entered hospital because of anæmia and vomiting. Hæmoglobin 5·6 g. per 100 ml. (reticulocytes 7·2%, platelets 79,000, bilirubin 3 mg. per 100 ml., direct Coombs test negative). No abnormal agglutinins were detected with the indirect Coombs test in saline and albumin at various temperatures. Paper electrophoresis revealed no gamma-globulin. The cause of this agammaglobulinæmia is unknown. It is unlikely that it was of a congenital hereditary origin. A right-sided hemiplegia developed and she expired, despite corticotrophin therapy, a month after admission. Necropsy showed the same changes as in case 1.

CASE 3.—A 52-year-old mason had two episodes of aphasia and mental disorientation followed by rapid deterioration, progressive pyramidal signs, purpura, jaundice, and death within 2 months of the onset of symptoms. Hæmoglobin 8 g. per 100 ml. (reticulocytes 23·5%, platelets 33,000, bilirubin 5·2 mg. per 100 ml.). Direct Coombs test negative. No abnormal agglutinins were detected in the indirect Coombs test at various temperatures in saline or albumin medium. L.E. test negative. Immunoelectrophoresis: no β_{2M}-globulins. The absence of this line is a constant finding in the antibody-deficiency syndrome. Necropsy confirmed the clinical diagnosis of T.T.P.

In addition to the association of T.T.P. with agammaglobulinæmia, the negative Coombs test in our patients and in the great majority of the published cases is further evidence that the hæmolytic anæmia is not the result of autoimmunisation. Furthermore it has never been possible to demonstrate platelet antibodies in T.T.P.

The pathogenesis of this curious syndrome remains an enigma. Theoretically, the underlying mechanism may be similar to that in the experimental generalised Sanarelli-Schwartzman reaction, in which the vascular lesions are identical to the ones observed in T.T.P. Thrombocytopenia is a feature of the experimental syndrome, but hæmolytic anæmia has not been observed. The development of T.T.P. within 24 hours of vaccination in case 1 could be compared to the effect of the provoking

4. Benson, F., Celander, O., Haglund, G., Nilsson, L., Paulsen, L., Rencks L. *Acta anæsth. scand.* 1958, **2**, 37.
5. Colgan, F. J., Eldrup-Jorgenson, S., Lawrence, R. M. *J. Amer. med. Ass.* 1960, **173**, 1557.

1. Frick, P. G., Hitzig, W. H. *Schweiz. med. Wschr.* 1959, **89**, 58.

injection of endotoxin in the experimental animal with the generalised Sanarelli-Schwartzman reaction.

Department of Medicine and Pediatrics, Kantonsspital, University of Zürich.
P. G. FRICK
W. H. HITZIG.

SIMPLE ULCERATION AND CANCER

SIR,—In your annotation of Dec. 10 you stress the growing acceptance of the view that there is a correlation between the two. You point out the frequency with which carcinoma follows ulceration of skin and colonic epithelium, but you regard the rarity of malignant change in duodenal ulceration as an anomaly.

The paradox can be explained readily on the assumption that cancer develops not merely because of the stimulus of chronic ulceration but as a result of the interaction of the stimulus and the genetic instability of the epithelium. The same stimulus may produce quite different effects on the epithelium of skin, duodenum, ileum, and colon. Neoplastic mutation is rare in the mucosa of the small bowel, and prolonged ulceration does not succeed in increasing materially its frequency. In the colon, however, carcinomatous mutation is common and the effect of longstanding ulceration is to increase the risk of malignant change about thirtyfold. The mechanism of this is unknown: it may be a direct chemical phenomenon or merely the result of increased rate of mitosis (and therefore increased chance of mutation) in the healing phase. It is significant that carcinoma develops most frequently in those patients whose colitis is in remission.

Regional ileitis has been observed for a sufficient length of time for it to be apparent that it is only rarely complicated by carcinomatous change. Only recently, however, has it been recognised that Crohn's disease not infrequently affects the colon. Cases of this type have been followed for only a few years. It would be anticipated that carcinoma will develop with a frequency similar to that in ulcerative colitis. The potentiality of the affected epithelium is more important than the disease producing the ulceration.

In view of the rarity of spontaneous carcinoma of the duodenum, jejunum, and ileum it is not surprising that chronic ulceration fails to induce neoplastic changes in them. The only anomaly is the rarity with which benign gastric ulcer is followed by carcinoma.

St. Mark's Hospital, London, E.C.1.
A. G. PARKS.

SIR,—Your annotation of Dec. 10 gives interesting clinical data on the part played by ulceration in the genesis of cancer.

I have carried out animal experiments at this hospital and my preliminary findings confirm your observations. It appears that three factors are involved in carcinogenesis:

(*a*) The exposure of the epithelial basal cells, such as would occur in certain anatomical sites, in acute ulceration, and in the early stages of wound repair.

(*b*) The direct access of an exogenous carcinogen to such a denuded area.

(*c*) The duration of contact between the cell and the carcinogen.[1]

In a series of experiments on rats' stomach carcinogens were administered by stomach tube or by local application via gastrostomy. A number of animals of the latter group were also subjected to chemical or surgical ablation of the gastric mucosa. In the experimental group this pretreatment was followed by topical administration of carcinogens, whereas the controls received gastric injuries only. There were no local tumours among 66 rats fed by stomach tube but several mammary tumours were elicited. Nor were there tumours among 14 rats whose stomachs were injured or ulcerated. Among 101 rats given carcinogens via gastrostomy with or without concomitant ablation of the mucosa, 10 animals developed gastric tumours including squamous, adeno, and anaplastic carcinomas. 2 tumours weighed as much as 80 g., and 4 yielded widespread metastases.

Your question regarding the paucity of cancers in duodenal ulceration may be answered by reference to the three criteria which, if combined, lead to the development of cancer. The passage of foodstuff varies in the different segments of the digestive tract, being rather slow in the stomach, colon, and rectum and fairly rapid in the first part of the duodenum. The possible mechanical or chemical irritants of the digested food would thus quite naturally affect ulcers in stomach, colon, or rectum more readily than those in the duodenum. Even quiescent lesions may, in their acute stage, have been affected by such irritants and the cancer arising therein may only become apparent after a long latent period.

I have carried out a number of other, similar, experiments on skin, cervix uteri, and tongue of laboratory animals and preliminary findings suggest the general applicability of the "three-criteria theory".

Marie Curie Hospital, London, N.W.3.
R. STEIN-WERBLOWSKY.

1. Berenblum, I., Haran-Ghera, N., Trainin, N. *Brit. J. Canc.* 1958, **12**, 402.

KIDNEY HOMOTRANSPLANTS

SIR,—Dr. Benirschke's plea (Oct. 29) for more extensive records of placentation was pertinent in the study of the relation of the type of placental circulation to the histocompatability status in twins. I wish to add a few isolated experimental findings to his comments.

In the course of recent experiments at the Postgraduate Medical School, London, the following incidental observations were made. Conventional rejection of skin homografts occurred in 10 cases (8 rats from one litter and 2 dogs from a single litter). The circumstances of placentation in these animals is, of course, unknown. However, it is extremely unlikely, at least in the rats, that there was vascular communication between adjacent placentas. The discrete placement of the sites of placental attachment along the uterine horns in rodents is well known and its mechanism has occasioned much research.

Apposed placentas are found [1] and can be induced [2] in the mouse; Ladman [3] demonstrated histologically the consistent presence of a septum of maternal connective tissue between the two placentas. The only real union of fœtal tissues found was that of contiguous Reichert's membranes; anastomoses between placental labyrinths or fœtal blood-streams was unlikely. In the rat, Huber [4] reported the presence of two egg cylinders in one decidual crypt; he regarded the occurrence as extremely rare. Carr [5] considered the discovery of a single case of placental fusion important enough to report. No mention of circulatory confluence between placentæ was made by Bøe [6–8] who made extensive and meticulous studies with indian-ink injection and corrosion preparations in the rat.

This evidence, though tenuous, supports Dr. Benirschke's contention to some degree, and emphasises the need for a precision in classifying multiple embryos such as recommended by Boyd et al.[9] and originally suggested by Hamlett et al.[10]

Boston, Mass.
JOHN ANDERSON.

1. Carr, J. G. *Proc. roy. Soc. Edinb. B*, 1945, **62** (part 2, no. 22) 189.
2. Smithberg, M. *Anat. Rec.* 1955, **121**, 368.
3. Ladman, A. J. *ibid.* **125**, 41.
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HOSPITAL INFECTION

SIR,—Your comments (Dec. 3) on a new and valuable book on hospital infection, include the statement that the "mode of transmission" of staphylococcal infection in hospital wards "is still obscure". This seems to me to be obscurantism or perhaps agnosticism in excelsis.

The staphylococci are carried into the ward in or on the bodies of patients and their attendants, and are distributed in the ward by the clouds of dust from bedmaking and brisk movements of persons in the wards. The stores of staphylococci are to be found in blankets (woollen), in the interior of mattresses and pillows, in floor dust, and in the noses of persons in the wards. In maternity wards infants' noses and umbilicuses are reservoirs of pathogenic staphylococci.

Blankets should be laundered at short intervals (every ten days in a maternity ward) and be sterilised while being washed. Mattresses and pillows should be treated in the hospital formalin disinfector, preferably every ten days. All attendants should wear effective sterile masks and gowns. The floors should be cleaned with effective vacuum cleaners, not brushed with brooms. To avoid transmission by their hands nurses should wear thin sterile rubber gloves. None of these precautions is difficult; nor should nursing routine be disturbed.

St. Margaret's Hospital, Epping. FRANK MARSH.

BENZHEXOL IN MULTIPLE SCLEROSIS

SIR,—The course of multiple (disseminated) sclerosis is seldom influenced by treatment, and the following case is recorded because useful, if slight, diminution in disability was achieved with drugs.

A married woman had retrobulbar neuritis at the age of 23 in 1943. In 1949 she had a normal pregnancy. In 1950 investigation for fatigue and weight-loss revealed no definite abnormality, but two years later multiple sclerosis was diagnosed on the basis of temporal-disc pallor, asymmetrical limb reflexes, extensor plantar responses, slight nystagmus, and a paretic Lange cerebrospinal-fluid curve.

When she came under my care in 1953, she tended to fall to the left on walking and had diplopia on looking to the left. In 1956 a left retrobulbar neuritis developed, followed by a right-sided attack; at this time frequency and hesitancy of micturition and awkwardness of the right foot also began. In 1957 paræsthesiæ developed in both lower limbs and her gait got worse, but with a stick she still walked half a mile to work each day. In September, 1959, she finally became housebound, needing the support of walls or furniture every two or three steps. During the previous eight years she had had, at various times, without benefit, injections of vitamin B_{12}, isoniazid, and nicotinic acid and prednisone.

In May, 1960, there was disc pallor, exaggerated tendon reflexes, ankle clonus, bilateral extensor plantar responses. The lower limb spasticity was much reduced when the patient lay down. She could stand unsupported even with her eyes closed, but not without much swaying; if, when standing, she looked downwards or to the left, she immediately lost her balance.

Her walking difficulty seemed to be due to loss of balance and lower-limb spasticity. Both factors were much influenced by posture, and as signs of general cerebellar involvement were slight, drugs acting on the vestibular apparatus or the basal ganglia seemed worth trying. Dimenhydrinate ('Dramamine') reduced frequency of micturition but gave no improvement in walking. On benzhexol hydrochloride ('Artane') (2 mg. q.i.d.) she reported blurring of vision for small print but improved mobility.

A double-blind controlled trial was carried out, using benzhexol, ethopropazine hydrochloride ('Lysivane'), trifluoperazine ('Stelazine'), and calcium lactate. A week's supply of each drug, with dosage instructions, was given to the patient in a sealed lettered envelope. The key was held by one of my partners, and the patient was told not to tell me the dose or colour of the tablets. The benzhexol was given in tablets of a different dose (5 mg. b.d.) to prevent its recognition. The patient was given a chart to record daily her walking capacity, bladder control, general sense of wellbeing, and any side-effects attributed to the tablets. She was seen at the end of each week's treatment. She took benzhexol 2 mg. q.i.d. until the eve of the trial.

Her first trial tablets proved to be calcium lactate. Her performance became much worse and, after a fall on the second day, her husband forbade her to take any more tablets. The second week, on ethopropazine, produced improvement, especially towards the end of the week; but in the third week, on trifluoperazine walking and mood deteriorated, a change possibly exaggerated by anxiety over her son's interview for a grammar-school place. In the fourth week, on benzhexol, her performance improved greatly. Though still relying on the walls and furniture, she could take two to three steps unaided and could move round the house more rapidly. None of the drugs had significant effect on bladder control.

There seems little doubt that her walking was improved by benzhexol and, to a lesser extent, by ethopropazine. Since the trial she has continued to take benzhexol (2 mg. 3–4 hourly during the day) and the effect persists.

London, N.W.5. ANTHONY RYLE.

PLACEBO EFFECT IN MENTAL NURSING

SIR,—The powerful therapeutic effect of placebos in general medicine is well known; and it has been shown [1] that chlorpromazine is only slightly more effective than placebos in chronic schizophrenia. As the behaviour of chronic mental patients is greatly affected by their nurses' attitude it seemed useful to discover if this attitude, too, is affected by the nurses' beliefs about the drugs their patients are having.

60 chronic female patients, 42 of them schizophrenic, who had been having an average daily dose of 210 mg. chlorpromazine for many months, were randomly divided into two groups. After a preliminary fortnight to establish a baseline, without any environmental changes, and to the knowledge of the pharmacist alone, group A was changed to placebo. Three weeks later group B was also changed to placebo. After a further week, when group A had been on placebo for a month, and group B for a week, the staff having believed them to be still on chlorpromazine, the nurses were told to administer a placebo; and a week later this was withdrawn and the patients knew themselves to be without medication.

The patients' behaviour at different periods of the trial was assessed by nursing reports of such disturbances as aggression, restlessness, insomnia, or withdrawal.

The number of reports of disturbed behaviour was:

Trial week	*Group A*		*Group B*	
	Medication	*Reports*	*Medication*	*Reports*
1	Chlorpromazine	4	Chlorpromazine	8
2	Chlorpromazine	6	Chlorpromazine	6
3	Substituted dummy	5	Chlorpromazine	9
4	Substituted dummy	5	Chlorpromazine	5
5	Substituted dummy	4	Substituted dummy	4
6	Substituted dummy	4	Substituted dummy	9
7	Prescribed dummy	17	Prescribed dummy	23
8	None	18	None	27

And the reports of disturbance during different periods were:

	Reports	*Patient-weeks*
Stabilised on chlorpromazine	42 in 200	(*21%*)
On dummy, unknown to patient or staff	27 in 150	(*17%*)
On prescribed dummy	40 in 60	(*66%*)
Chlorpromazine and dummy withdrawn	37 in 60	(*61%*)

These results indicate that the (unknown) substitution of a placebo produced no deterioration; but that, with the nurses told to use a placebo, reported disturbances increased threefold. 6 patients were described as unmanageable, dramatic regressive behaviour was demonstrated, and a return to chlorpromazine was requested; a further 4 patients were so described in

1. Salisbury, B. J., Hare, E. H. *J. ment. Sci.* 1957, **103**, 830.

the last week without drugs. No greater instability was manifested in group A, although this group was off chlorpromazine for longer than group B.

It is clear that patients became more disturbed when nurses were aware of drug withdrawal. So either there was a continued benefit after chlorpromazine withdrawal which was overriden by the effect of nurse anxiety, or the only action of the drug at any time was its placebo effect. The results are not surprising as the sisters involved were uniformly of the opinion that the introduction of chlorpromazine had reduced the use of sedatives, E.C.T., and leucotomy and made easier the free management of patients. But in one ward whose sister had predicted that no ill-results would follow withdrawal there was no rise in disturbances, while in another whose sister foretold a recurrence of aggression and destruction, and threatened to resign, disturbances rose from 1 to 17 a week.

A placebo normally symbolises to the patient his doctor's care.[2] In hospital it may also stand for the nurse as a protection against the patient's demands; and withdrawal of this protection may lead to emotional insecurity on both sides. Tranquillity in the chronic mental patient may depend more on nursing than on tranquillisers.

I am grateful to May & Baker Ltd., for the supply of blank pills, and to Miss I. Lumb, hospital pharmacist, for her cooperation.

Warlingham Park Hospital, Surrey. M. K. LE VAY.

A SIGN OF SURGICAL EMPHYSEMA

SIR,—The well-established courtesy of a spoken greeting from one's patient has a special diagnostic significance in a thoracic unit; it serves to indicate the presence of surgical emphysema arising from the chest far earlier than any other method of examination. A peculiar nasal intonation is heard.

Although loosely to be described as a " stuffy nose ", only once has it been mistaken for this in several hundred observations; the note is somewhat flatter, and the patient is commonly unaware of the change in his speech. For a number of years this sign has been infallibly noted and indicates the presence of surgical emphysema of even small degree not yet noted by the nursing staff. Its only prerequisite is that the patient shall have been sitting up; the small areas of emphysema often noted in the region of thoracoscopy stabs were not associated with the sign since in such cases the patients were commonly nursed lying with the affected side uppermost. Surgical emphysema in an upright patient has never been noted without this sign, which occurs long before the characteristic " bloated-face " appearance. In most minor degrees of the condition, a certain training based on grosser experiences of it is necessary to recognise the faint change in voice.

Only three mechanisms suggest themselves. Venous obstruction, leading to turbinate congestion, is most unlikely, since it is not appreciated visibly, neither does the same voice appear in cases of recognised venous congestion or obstruction. Lymphatic obstruction, due to tissue separation by air, to which the turbinates are unduly susceptible, cannot be refuted; but the most likely cause is that air simply rises in the tissue planes and causes a local congestion of both venules and lymphatics immediately around the turbinates. In all cases, small " pockets " of surgical emphysema can be palpated at the root of the neck, provided the search be thorough, even though the amount there be slight and the maximum degree elsewhere.

Modesty does not caution a claim for originality in the description of this bedside sign, since it is one of almost no clinical value!

King Edward VII Memorial Chest Hospital, Hertford Hill, near Warwick. J. C. A. RAISON.

2. Wolf, S., Pinsky, R. H. *J. Amer. med. Ass.* 1954, **155**, 339.

Parliament

Administration of Queen Mary's Hospital, Roehampton

AT the end of question time on Dec. 12, Mr. ENOCH POWELL, the Minister of Health, made the following statement:

" With the agreement of the boards of governors of Queen Mary's Hospital, Roehampton, and of Westminster Hospital, I have decided, subject to consultation with London University, and to any necessary consultation with the Charity Commission by the Roehampton governors, to transfer the administration of Queen Mary's Hospital from my department to the board of governors of Westminster Hospital.

" The separate identity of Roehampton will be maintained and war-pensioners will continue to have the same priority as at present. I shall add to the Westminster board not less than three members representative of the Roehampton governors and of the ex-Service interests. The governors and the ex-Service interests will also be substantially represented on the house committee of the hospital. The services now provided by the Roehampton governors will, of course, not be affected, and the administration of the limb-fitting centre will remain the responsibility of my department.

" The arrangements which I have announced will give the Roehampton governors and the ex-Service interests a direct share, which they have hitherto not had, in responsibility for running the hospital, and should guarantee the maintenance of its unique status."

Dr. EDITH SUMMERSKILL: While I have no objection to the Minister's statement, can he tell the House why it has been necessary to make this change?—Mr. POWELL: The proportion of ex-Service men occupying beds at Roehampton has been falling and is now only about a third of the total. In these circumstances, it seemed right that new arrangements should be made if the unique status of the hospital and the priority of the ex-Serviceman were to be absolutely safeguarded.

QUESTION TIME

Drug Prices

Lord BALNIEL asked the Minister whether he would make a statement on the renewal of the voluntary scheme for the regulation of drug prices.—Mr. POWELL replied: Agreement has been reached with the Association of British Pharmaceutical Industry on a number of modifications to the scheme and it is to be renewed, as modified, until June 30, 1964. The main modifications, all of which should result in further restraint on prices, are as follows:

(i) Provision is made for the prices of some widely used patented drugs to be negotiated directly.

(ii) The percentage of sales that must be exported if the export price is to be the maximum price is increased from 20 to 25.

(iii) The formula which fixes the maximum price for products which do not satisfy the export criterion, and for which there are no exact unbranded equivalents, is revised so as to result in lower maxima.

(iv) The definition of new drugs, which are free from control during their first three years, is so revised as to exclude products which manifestly owe nothing to fresh research.

I should like to acknowledge the cooperation of the Association in the discussions that have led to agreement on these modifications.

R.C.P.'s New Building

Mr. G. JOHNSON SMITH asked the Minister of Housing and Local Government and Minister for Welsh Affairs whether the plans for the proposed new building for the headquarters of the Royal College of Physicians, on the east side of Regent's Park, had been approved by him.—Mr. HENRY BROOKE replied: This proposal has been referred to me by the London County Council because it constitutes a departure from the approved development plan, in which this area is allocated for residential use. It involves the demolition of Someries House, which was originally designed by Nash as an adult orphanage,

but little remains of his design; it has been extensively altered and is now used as Government offices. In 1946 the Gorrell Committee reported that this building could and should be demolished. This view was accepted by the Crown Estate Commissioners, who decided to choose a skilled developer, advised by an architect, acceptable to them, to redevelop the site in harmony with the surrounding Nash buildings and terraces.

The scheme of redevelopment has been prepared by Messrs. Denys Lasdun and Partners for the college. The Royal Fine Art Commission says that it is well satisfied with the design: it feels that it would be acceptable as a neighbour to the regency buildings which are to be preserved. The Crown Estate Commissioners have given their consent to the plans. It is intended that all the trees on the western boundary facing Regent's Park shall be retained. The St. Pancras Borough Council has no objection, subject to questions of access, and the London County Council is disposed to grant planning permission. Before I authorise it to do so, I have arranged for a small model of the building and its setting to be exhibited for a week, so that Members may have the chance to see the design for this important proposed building and its relationship to the Nash terraces.

Strontium and Leukæmia

Mr. R. W. SORENSEN asked the Minister of Health, as representing the Minister for Science, to what extent an increase in the presence of strontium and leukæmia had been detected in infants, children, young people, and adults, respectively, during the past two years.—Mr. POWELL replied: The average levels of strontium 90 measured in bone during 1959 as a whole show some increase on those recorded during 1958 for still-born infants, children, and young people, but there was relatively little change from the first to the second half of 1959. I regret I can only give figures for deaths from leukæmia. In the age-groups 0–4, 5–14, 15–24, and 25 upwards these were 141, 192, 95, and 1958 in 1958, and 152, 219, 124, and 2039 in 1959.

Mr. SORENSEN: Is it not true that the figures for leukæmia show a serious increase?—Mr. POWELL: The figures for leukæmia, unfortunately, have been on the increase for the past 30 or 40 years. There is no clear reason for connecting the two matters to which this question refers.

Hospital Underspending

Mr. H. J. BOYDEN asked the Minister what amount of underspending he anticipated in the capital programme of the hospital authorities this financial year.—Mr. POWELL replied: Returns earlier in the year showed some underspending, but hospital boards were authorised to undertake additional works. I cannot anticipate the final outturn. Mr. BOYDEN: Is it not rather deplorable that when the Government set out at last to improve the hospital service and increase the amount of hospital building they should, almost before it starts, be caught by underspending?—Mr. POWELL: I am anxious to spend, if possible, every penny of my capital estimate, and I have for example, in the Newcastle region authorised a further £500,000 of capital work.

Disinfestation of Aircraft

Mr. F. E. NOEL-BAKER asked the Minister what steps he had taken to ensure that all aircraft were properly disinfected and cleared of flies and other insects before or on arrival at United Kingdom airports.—Miss EDITH PITT replied: All civil aircraft coming from countries outside the Western European Union and the Republic of Ireland must declare on landing when and where they were last disinfected and cleared of insects. The health authority then decides what further action to require on grounds of health. Mr. NOEL-BAKER: Can the hon. Lady give a categorical assurance that the Word Health Organisation recommendations about aircraft disinfestation are being rigidly applied at all British airports? Further, is she satisfied with the procedure laid down by the W.H.O., and are we in fact taking advantage of the most up-to-date and effective insecticides which are available for this work?—Miss PITT: Past experience has shown that the risk of introducing infectious diseases into this country by aircraft is very small. Disinfecting or disinsecting on arrival in the United Kingdom is not normally necessary since in some circumstances—for example, in yellow-fever-infected areas—the international sanitary regulations require, among other sanitary measures, the disinfection or disinsecting of the aircraft before departure, and in any case no vector-borne quarantinable disease exists in this country and public-heath measures would prevent its spread were it introduced.

Home-helps

Mr. N. N. DODDS asked the Minister, in view of the increasing practice of local authorities demanding payment for the provision of home-helps to those in receipt of National Assistance, what progress had been made in discussions with associations representing local health authorities to stop this practice; and what action he had taken to assist such people meanwhile.—Miss PITT replied: The Association of Municipal Corporations has now advised its members that it considers this practice unjustifiable; discussions with the County Councils Association are continuing. Meanwhile I understand that the National Assistance Board's officers use their discretionary powers where necessary to ensure that the payment of such a charge does not leave a recipient of assistance with less income than the National Assistance standard.

Social Workers

Mr. KENNETH ROBINSON asked the Minister if he accepted the recommendation in the Younghusband report concerning financial assistance from central Government funds for the training of social workers; and when he intended to introduce the necessary legislation.—Mr. POWELL replied: I consider that the present arrangements for financial assistance to trainees should be given a fair trial before further steps are contemplated. Mr. ROBINSON: Is not the Minister aware that the Younghusband Working Party, which gave a good deal of thought to this matter, came to the exactly opposite conclusion and thought that the present arrangements would not be suitable for the expansion of training? Will he not give this matter further thought before reaching a final decision?—Mr. POWELL: This is not a final decision. I am sure that at present the number of trainees is not limited by the absence of any Exchequer grant, and so it seems reasonable to see how the present arrangements work.

Mr. G. T. SWINGLER asked the Minister what steps he was taking to increase the number of psychiatric social workers in the National Health Service. Miss PITT replied: Facilities for training have been provided at two further universities this year, but availability of experienced supervision remains the limiting factor and this can only improve gradually. Mr. SWINGLER: Is the Parliamentary Secretary not aware of the desperately serious shortage in so many areas, which calls for the most urgent and drastic steps in schools and universities to recruit more people, and for the greatest effort on the part of those who are qualified to give the training?—Miss PITT: There is no shortage of applicants. As I indicated in my answer, part of the training is actual case-work—practical work—and that needs an already qualified psychiatric social worker in order to undertake the training of recruits to the service, but steps have been taken to improve the position.

Venereal Disease and Young People

Dr. DONALD JOHNSON asked the Minister what steps he was taking to counteract the increased incidence of venereal disease amongst young people. Mr. POWELL: Local health authorities, hospitals, and general practitioners were reminded last year of their responsibility to cooperate in efforts to reduce the incidence of venereal disease generally, but I am not satisfied that we yet understand sufficiently the significance or causes of the increase amongst young people, and I am considering how these can best be investigated. Dr. JOHNSON: Does the Minister not agree that this is an extremely serious problem owing to the new drug-resistant strains of infection that are about, and, while moral objugations in these days are unfortunately rather discounted, does he not consider it within his scope at least to emphasise the virtues of personal cleanliness, which have lapsed in so many instances at the same time as other virtues?—Mr. POWELL: I am not sure that moral

objugations come within the scope of my department, but I am sure that all those concerned understand the importance of emphasising the right rules upon all those with whom they come in contact.

Family Planning Poster

In answer to a question asking if the Government approved of the action of the British Transport Commission in ordering the removal of a perfectly harmless Family Planning Association advertisement, Lord CHESHAM replied: My Lords, I am told that the poster was withdrawn by the British Transport Commission because it was controversial on religious grounds. The responsibility for such decisions rests with the Commission, and the Government do not seek to influence or express any opinion on them.

Lord SHEPHERD: My Lords, is it not remarkable that this advertisement, which had no controversial or objectionable matter in it, which had been fully accepted by the Board four or five months ago, and which was issued by a very responsible organisation, should now be removed, bearing in mind that dubious advertisements are still being shown on the railways in London? Does the noble Lord not remember that a similar attempt was made in this House to prevent the Family Planning Association from appealing for funds on the B.B.C., and on that occasion the Board of the B.B.C. stood firm? Is it not against all tolerance that this should happen, and is it not more an arrogant attack on liberty?

Lord CHESHAM: My Lords, I do not believe this is an arrogant attack on liberty at all. So far as I am aware no-one has suggested—at least, I have not been told so—that this poster was in any way offensive in itself. The poster itself is not exceptionable, but I am informed by the British Transport Commission that they have received letters objecting to the poster on religious grounds. I think I should remind the noble Lord of Rule 18 of the Commission's regulations regarding advertisements which they cannot accept. Rule 18 deals with posters.

"which refer to religious or sacred subjects in a manner which might give offence or contain matter or illustrations likely to be construed as religiously controversial."

Evidently this poster was so considered, and the British Transport Commission, it appears, saw fit to withdraw it on those grounds.

Charge for Road Casualties

Lord STONHAM asked the Government if they would abolish the obligation which rests on hospitals to collect an emergency treatment fee of 12*s*. 6*d*. in respect of persons who require treatment as the result of a road traffic accident. Lord NEWTON replied: My Lords, hospital authorities are entitled to these fees and they therefore have a duty to claim them. Any changes in the obligation imposed on vehicle users by the Road Traffic Act to pay these fees on a claim being made would require legislation, and this is a matter which the Minister of Health will bear in mind at the appropriate time. Lord STONHAM: My Lords, whilst I welcome the information that this matter is being borne in mind, may I ask whether the noble Lord is aware that the cost to hospitals of collecting this fee is very considerably more than 12*s*. 6*d*.; that it involves a great deal of work for the police, and that the motorist, who has to pay it, thinks it grossly unfair, because often he is not responsible for the accident. This imposition is unfair; it costs more than we receive, and it would be in the interests of the Treasury to abolish it. Lord NEWTON: My Lord, perhaps I should be summarising the views of the noble Lord if I were to say that he regards this fee as anomalous in a great many ways. If that is so it has been anomalous for a long time, because this provision for payment of a fee dates from 1934. There was an opportunity to abolish it, as the noble Lord would like, during the passage of the National Health Service Act in 1946, but it was not abolished; and in fact the provision was actually continued in the tenth schedule to that Act. I am not promising that, when the appropriate time comes, my right honourable friend will do what the noble Lord wants; on the other hand, I am not shutting the door on that.

Lord STONHAM asked the Government whether, in view of the great amount of work falling on hospital staffs from the present system of collecting from insurance companies treatment charges in respect of persons injured in road accidents, they would negotiate an agreement with the companies whereby they pay to Her Majesty's Treasury a lump sum based on premium income, which would be the estimated equivalent of the present sums they pay for the treatment of injured persons in hospital.—Lord NEWTON replied: My Lords, as the Road Traffic Act, 1960, specifies who should make, and who should receive, these payments it would be necessary to amend the Act to make legal any other method of collection. But the Minister of Health will bear in mind, at the appropriate time, the noble Lord's suggestion. Lord STONHAM: When it is being considered, will the noble Lord have regard to the fact that the average recovered in any one year from all these charges is about a third of a million pounds—it was £350,000 last year—and that, in view of the great cost to hospitals, and the tremendous time it takes to agree these claims with the insurance companies, we should be making a great bargain if we got a quarter of a million pounds from them?—Lord NEWTON: My Lords, I am sure my right honourable friend will bear that point in mind also.

Obituary

DONALD WHATLEY ROY

M.A., M.B. Cantab., F.R.C.S., F.R.C.O.G.

Mr. Donald Roy, consulting obstetric surgeon to St. George's Hospital, London, died at York on Dec. 9 at the age of 79.

He was born at Appleton Roebuck, York, and his father, the Rev. James Roy, was the rector of Stockton-on-Forest. From St. Peter's School, York, he went to Sidney Sussex College, Cambridge, as an exhibitioner and scholar. He took first-class honours in both parts of the natural sciences tripos and at St. George's Hospital he won the university scholarship and the Brodie prize for clinical surgery. After qualifying in 1906 he held resident appointments at the General Lying-in Hospital, York Road, at the Royal Free Hospital, and at George's where he became in due course obstetric tutor and registrar. In 1913 he was appointed to the staff of the Samaritan Hospital for Women. During the 1914–18 war he served at first as a surgeon in the R.N.V.R. with the Grand Fleet. In 1917 he transferred to the R.A.M.C., and from 1917 to 1918 he was in charge of the surgical division of the Northamptonshire War Hospital. Soon after his return to civilian practice he joined the staff of George's. He was an examiner for the Universities of Cambridge and London, the Royal Colleges, and the Society of Apothecaries. For some time he was a member of the University's Board of Advanced Studies and of the London Hospitals Representative Committee. Earlier he was consulting obstetrician to the London County Council hospitals. His published work included articles on the teaching and organisation of midwifery and contributions to several textbooks. He was elected F.R.C.O.G. in 1929.

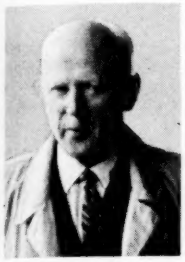
C. M. G. writes:

"To those who worked with him, Dr. Roy was a great man. His intense devotion to detail will always be remembered by them as the outward and visible evidence of the integrity that they came so wholeheartedly to respect and admire. His basic ideas of pelvic surgery were ahead of his time and it is regrettable that his active life did not last sufficiently long for him to see their general acceptance. As an operator, he strove for an almost inhuman perfection, sparing none of his assistants, and still less himself. As a teacher, he was more revered in retrospect than at the actual moment of instruction and this was largely due to his disarming modesty. The courage with which he faced the physical disasters of his middle age roused the wonder of those who knew it, and it is greatly to be regretted that he was never given the recognition that his great qualities deserved."

Mr. Roy married Beatrice Anne, daughter of Henry Barstow. She survives him with two sons and a daughter.

SERGEI TERNOVSKY
M.D.

Professor Ternovsky, who was chief of pædiatric surgery in the Second Moscow Medical Institute (the Institute), Pirogov died on Nov. 19. His book on the surgery of childhood, based on his lectures for students at the institute, first published in 1949, has become a standard textbook in Russia and is now in its third edition. His chief surgical interests were renal disease, including calculi and ectopia vesicæ, congenital abnormalities of the alimentary tract, and bone and joint surgery, especially osteitis. He was made a member of the Academy of Medical Sciences in recognition of his work, and had lately been elected a member of the British Association of Pædiatric Surgeons.



R. B. Z. writes:

"A charming and cultured man in his early sixties, Professor Ternovsky has been a notable figure at pædiatric surgical meetings in eastern Europe over the past few years. His quiet, constructive, and critical contributions to discussion were the more welcome because of the patently friendly, and often humorous, vein in which they were given. He spoke French and German well and had a far greater command of English than he cared to admit, so that in a cosmopolitan crowd his wide interests found a ready and sympathetic response. He will be greatly missed at a time when his integrity and ability made him an outstanding, if unofficial, ambassador of his country. Pædiatric surgery has lost a brilliant technician, a wise doctor, and a kind man."

CHARLES ALFRED BIGNOLD
M.A., M.B., B.Sc. Edin.

Dr. Charles Bignold, formerly medical officer of health for Ayrshire, died at his home in Ayr on Dec. 1 at the age of 75.

Born and bred in Ayr, he held no parochial outlook. Though his undergraduate career at Edinburgh was early directed towards public health, he served in the R.A.M.C. as a regular officer before the outbreak of the 1914–18 world war, and went at once to France with a field ambulance. He saw arduous service at the battle of Mons and in the subsequent retreat, on the Marne, and on the Aisne. Invalided from France, he later served in India. Returning at the end of the war to civilian life, he eventually joined the public-health department of the county of Ayr. He became county M.O.H. in 1926 and held this position until he retired in 1950.

W. I. C. M. writes:

"Dr. Bignold was a quiet, modest man with a keen sense of humour, in which there was a vein of gentle cynicism. It must be confessed that those whose ideas or actions were subjected to his amused probing did not always relish this attention, but his qualities were given full recognition by Ayr County Council, which, with his advice, gained in medical matters a reputation for being progressive second to none in Scotland. Probably he himself regarded the early success of his diphtheria immunisation campaign as his greatest personal contribution to public health, but maternity and child welfare and the school medical and dental services all received direct and practical encouragement from him. He was a leader in the experiment of appointing whole-time clinical specialists to work in local-authority areas. An obstetrician was appointed in 1937 and later a chest physician and a pædiatrician. It ill behoves one of these specialists to speak of the success of these appointments, though this has been commented on elsewhere. Suffice it to say that when the National Health Service was in the planning phase, one at least of the whole-time specialists viewed with apprehension the discontinuance of a working association which had been satisfying professionally, and which on the personal side had been happy, respectful, and even affectionate.

"Dr. Bignold's happy home life was appreciated by those fortunate enough to be admitted to his personal friendship. His wife only survived him for a few days and died on Dec. 12. They leave a general practitioner son, and a daughter now a sister at the Ayrshire Central Hospital, itself a memorial to her father's vision and skilled planning."

Major-General D. C. MONRO

J. M. W. writes:

"Monro started the field surgical units to deal with the long lines of communication in the advance of the 8th Army to Tunisia, and he has been called the 'Father' of these units, which is very true. These small units moved forward with the advancing troops and were able to give surgical treatment to many of the wounded at a very early stage. He also developed the Tobruk plaster splint which was used in the evacuation of lower-limb fractures with great success. Jock Monro was a great character. He was an excellent surgeon and one of the neatest operators I have ever seen. He was a first-class administrator. He knew all the surgeons in the Middle East Force and was trusted and respected by everyone. He was good at most games, first-class at golf, and an enthusiastic small-boat sailor. He had a great fund of humour, and was excellent company. It is a sad thought that we shall not meet Jock again."

Dr. G. F. T. SAUNDERS

M. H. H. writes:

"Dr. G. F. T. Saunders was no publicity hunter, but those who saw him at work came away with a profound respect for his knowledge and meticulous thoroughness. It was a remarkable experience to go round the village of Kintampo with him; for many years he was the only European living there, and he appeared to know everyone and was usually followed, like the pied piper, by a throng of smiling children. He had a way of convincing his colleagues that he genuinely valued and wanted their opinions, but his charming humility in this respect concealed an encyclopædic knowledge of medicine and many other subjects. It was typical of Saunders that in 1928, before anybody had reported onchocercal blindness in Africa, he commented in a departmental report that it was strange to find the same belief in the Lawra-Tumu district of the Gold Coast that was held by the natives of Guatemala about the dangers of blindness in association with *Onchocerca* nodules on the head. By the death of this charming and erudite man the people of Ghana have lost a devoted servant."

Appointments

BEARE, R. L. B., M.B. Lond., F.R.C.S.: consultant plastic surgeon, St. Mary's Hospital, London, and plastic surgery and jaw injury centre, Queen Victoria Hospital, East Grinstead.

BIRNSTINGL, M. A., M.S. Lond., F.R.C.S.: consultant surgeon in charge of clinic for peripheral vascular disorders, Royal National Orthopædic Hospital, London.

BRUCE, R. J., M.B. Aberd., D.M.R.D.: consultant radiologist, South and North Tees-side groups of hospitals.

DACRE, A. J. I., M.B. Lond.: S.H.M.O., Rampton Hospital, Retford, Nottinghamshire.

LINFOOT, C. W., M.B. Durh.: assistant physician (S.H.M.O.), geriatric unit, Newcastle upon Tyne hospital group.

PLOWRIGHT, NELLIE M., M.B. Birm., D.C.H., D.P.H.: senior M.O., Portsmouth.

SPENCER, PAMELA M., M.B. Lond., F.R.C.S., M.R.C.O.G.: second honorary gynæcologist, Italian Hospital, London.

The Hospital for Sick Children, Great Ormond Street, London:

CAPPS, F. P. A., M.B. Lond., D.OBST.: house-physician.

GILCHRIST, G. S., M.B. Glasg.: house-physician.

GUPTA, J. S., M.S. Lucknow, F.R.C.S., D.O.M.S.: part-time M.O., ophthalmic department.

News

University of Oxford

On Dec. 10 the following degrees were conferred:

D.M.—R. M. Bannerman.
B.M.—I. G. McGill, T. N. Miller, D. H. Myers, T. H. D. Arie, J. B. P. Stephenson, Peter Husband, G. E. G. Sladen, Chester White, W. J. Appleyard, Gerassimos Spyros Spathis, J. E. Cawdery, J. S. Smith, T. S. Low-Beer, H. P. Berg, D. P. G. Bolton, R. G. Hett, R. A. L. Sutton, J. W. Baker, J. B. Wood, R. V. Clements, L. R. C. Bain, J. R. W. Christie Brown, T. W. Meade, Charles Rowlatt, J. M. Gumpel, M. A. Lee, C. E. Taylar, A. K. McKinlay, S. H. Milton, H. M. B. Busfield, Anne M. Waring, Sylvia N. Clayton, Gillian R. Sutton, Pamela F. Hull, Anne C. Maddocks, Gillian M. Roberts, Elizabeth J. E. Neale, J. L. Nicholas; D. L. Wingate, John Kenwright, S. R. Meadow, J. S. Meyrick, John Millward (in absentia).

University of London

Dr. M. D. Milne, lecturer at the Postgraduate Medical School of London, has been appointed to the chair of medicine at Westminster Medical School.

Dr. Milne, who is 45 years of age, graduated B.SC. from the University of Manchester in 1936 and M.B. three years later. From 1940 to 1945 he served with the 8th Army in field units. In 1946 he returned to Manchester and was house-physician and registrar at the Royal Infirmary. In 1950 he was appointed lecturer in medicine at Manchester University, and he proceeded to the degree of M.D. the following year. He took up his present appointment at Hammersmith in 1952. He was elected F.R.C.P. in 1958. His published work has dealt mainly with renal disease and disorders of metabolism.

The title of professor of oral medicine has been conferred on Dr. R. V. Bradlaw in respect of his post at the Institute of Dental Surgery, of professor of biophysics as applied to medicine on Dr. L. F. Lamerton in respect of his post at the Institute of Cancer Research: Royal Cancer Hospital, of professor of occupational psychology on Mr. Alec Rodger in respect of his post at Birkbeck College, and of professor of physical anthropology on Dr. N. A. Barnicot in respect of his post at University College.

University of Aberdeen

On Dec. 14 the following degrees were conferred:

M.D.—Eleanor M. Adams (with commendation).
M.B., Ch.B.—M. L. G. Addison, Alan Bremner, G. M. Bruce, D. S. Gill, Gordon Jamieson, Roy Mercer, Audrey F. Stewart, Mary M. Sutherland.

University of Edinburgh

The university court is to administer as a trust fund the J. J. M. Shaw Cancer Research Fund (Cancer Control Organisation for Edinburgh and South-East Scotland) of about £30,000. The capital and income of the fund are to be applied at the discretion of the university for research into the causes and treatment of malignant disease and, in particular, to provide fellowships or travelling scholarships.

Dr. Bruce Mackay has been appointed to a lectureship in anatomy, and Dr. R. G. S. Leask to a lectureship in clinical chemistry.

Royal College of Physicians of London

Dr. Louis Forman will deliver a Watson Smith lecture on Tuesday, Jan. 10, at 5 P.M., at the college, Pall Mall East, S.W.1. He will speak on the reaction of the skin to certain metals.

British Institute of Radiology

The annual congress of this institute will be held from April 26 to 28 at Church House and Central Hall, London, S.W.1.

Wanted in the Congo

The World Health Organisation is urgently seeking to recruit more staff, all of whom must speak fluent French, for the health services in the Congo.

There are over 100 vacancies for physicians, surgeons, anæsthetists, microbiologists, public-health officers, pharmacists, radiographers, and field and laboratory technicians at salaries ranging from $3600 to $7300. The candidates are being recruited by W.H.O. on the assumption that they may after a suitable period be offered long-term contracts by the Congolese Government. All interested should write for full details to the regional director, W.H.O., 8, Scherfigsvej, Copenhagen, Ø, Denmark.

London Jewish Hospital Medical Society

A meeting of this society will be held on Thursday, Dec. 29, at 8.15 P.M., at 11, Chandos Street, London, W.1, when Dr. C. O. Carter will speak on Advice to Parents on Genetic Risks.

Society for Psychosomatic Research

This society is offering a prize of £50, given by the Sir Halley Stewart trust, for original observations on a psychosomatic theme studied in patients seen in general practice. Entries should be sent to the secretary, 96, Portland Place, London, 1, by Dec. 1, 1961.

British Occupational Hygiene Society

A meeting on health physics is to be held by this society on Wednesday, Jan. 4, at 10 A.M., at the London School of Hygiene, Keppel Street, London, W.C.1. In the morning there will be a discussion on personal radiation dose measurements and in the afternoon on environmental measurements. Further particulars may be had from the hon. publicity officer, Dr. J. S. McLintock, Medical Service, National Coal Board, Hobart House, London, S.W.1.

Medical Academy in Singapore

This body, which specialists in all branches of clinical medicine set up in Singapore in 1958 under the title of the Academy of Physicians and Surgeons, has changed its name to Academy of Medicine. The office-bearers for 1960–61 are:

Master, Mr. D. W. C. Gawne; assistant master, Dr. Gwee Ah Leng; scribe, Dr. Ho Yuen (General Hospital, Singapore, 3); bursar, Dr. N. C. Sen Gupta; bedel, Mr. J. A. Jansen; censors, Prof. G. A. Ransome, Prof. G. S. Yeoh, Mr. D. R. Gunn, Dr. Khoo Oon Teik, Mr. Y. Cohen.

Institute of Diseases of the Chest, London

Clinical demonstrations for doctors will be arranged by Dr. K. M. Citron on Fridays from Jan. 13 to March 24. Open lectures will be given on Wednesdays from Jan. 11 to March 22 by Sir Russell Brock, Dr. N. Lloyd Rusby, Mr. W. P. Cleland, Dr. F. P. Lee Lander, Mr. J. R. Belcher, Dr. E. H. Hudson, Dr. J. H. Scadding, Mr. L. L. Bromley, Dr. R. V. Gibson, Mr. Donald Barlow, and Dr. Lynne Reid. All the lectures will be held at 5 P.M. at the institute, Brompton Hospital, Fulham Road, S.W.3.

New Headquarters for W.H.O.

Representatives of the Swiss Confederation, the Republic and Canton of Geneva, and the World Health Organisation on Dec. 5 signed formal agreements concerning the construction of the new headquarters building for W.H.O. in Geneva.

The agreements provide for an interest-free loan of 20 million Swiss francs granted by the Confederation, and another of 10 million Swiss francs at a nominal interest granted by the State of Geneva. The site, known as "Chautagnes", is in the commune of Pregny-Chambésy. M. Jean Tschumi, professor of architecture at the École Polytechnique de Lausanne, has designed the new ten-storey building, which is to cover an area of 16,425 sq. m. It is to have a "curtain" façade composed of glass walls with aluminium sunbreak elements on a framework of reinforced concrete covered with marble.

A meeting of the medical group of the Royal Photographic Society of Great Britain will be held on Thursday, Jan. 5, at 7 P.M., at 16, Princes Gate, London, S.W.7, when Mr. Charles Engel and Mr. John Brace will speak on closed-circuit television in medical diagnosis, research, and teaching.

CORRIGENDUM: *Anticoagulant Therapy*.—An error is contained in the opening of our account (Dec. 3, p. 1247) of this symposium. Dr. R. P. Biggs said that the coumarin anticoagulant drugs cause a fall in the blood-level of factor VII (*not* VIII), IX, and X.

Births, Marriages, Deaths

BIRTHS

WILEY.—On Nov. 22, at the Western Hospital, Toronto, to Pamela, wife of Dr. A. M. Wiley—a son.